Pulmonary Function Levels as Predictors of Mortality in a National Sample of US Adults

Lucas M. Neas and Joel Schwartz

Single breath pulmonary diffusing capacity for carbon monoxide ($D_{LCO}$) was examined as a predictor of all-cause mortality among 4,333 subjects who were aged 25-74 years at baseline in the First National Health and Nutrition Examination Survey (NHANES I) conducted from 1971 to 1975. The relation of the percentage of predicted $D_{LCO}$ to all-cause mortality was examined in a Cox proportional hazard model that included age, sex, race, current smoking status, systolic blood pressure, serum cholesterol, alcohol consumption, body mass index, percentage of predicted forced vital capacity (FVC), and the ratio of forced expiratory volume at 1 second (FEV$_1$) to FVC. Mortality had a linear association with the percentage of predicted FVC (rate ratio (RR) = 1.12, 95% confidence interval (CI) 1.08-1.17, for a 10% decrement) and a significantly nonlinear association with the percentage of predicted $D_{LCO}$ with an adverse effect that was clearly evident for levels below 85% of those predicted (RR = 1.24, 95% CI 1.12-1.37 for a 10% decrement). The relative hazard for the percentage of predicted $D_{LCO}$ below 85% was not modified by sex, smoking status, or exclusion of subjects with clinical respiratory disease on the initial examination. This association with the percentage of predicted $D_{LCO}$ was present among 3,005 subjects with FEV$_1$ levels above 90% of those predicted. Thus, pulmonary diffusing capacity below 85% of predicted levels is a significant predictor of the all-cause mortality rate within the general US population independent of standard spirometry measures and even in the absence of apparent clinical respiratory disease. Am J Epidemiol 1998;147:1011-18.

Pulmonary function testing has been recognized as an important indicator of life expectancy since 1846 (1). In recent prospective studies in Boston, Massachusetts, and Honolulu, Hawaii, lower levels and rapid declines of forced expiratory flows were associated with increased rates of all-cause mortality even after adjustment for cigarette smoking (2, 3). In a US national cohort, a ratio of forced expired volume at 1 second (FEV$_1$) to forced vital capacity (FVC) of less than 70 percent was associated with increased mortality (4). Single breath pulmonary diffusing capacity for carbon monoxide ($D_{LCO}$) is a measure of the lung’s capacity for gas exchange that has not previously been evaluated as a determinant of all-cause mortality. Each $D_{LCO}$ measurement involves the inhalation of air containing a known concentration of carbon monoxide, a 10-second breath-hold, and the measurement of the remaining concentration of carbon monoxide in the exhaled breath. Compared with simple spirometry, the measurement of $D_{LCO}$ is complex and time consuming and has a coefficient of variation that is considerably larger than the more standard forced expiratory maneuver. The current study examines pulmonary diffusing capacity as a predictor of all-cause mortality in a representative sample of US adults. The analysis controls for forced expiratory volumes and flows and considers the potential for nonlinear relations and the effects of collinear variables in the model.

MATERIALS AND METHODS

Sampling frame

The First National Health and Nutrition Examination Survey (NHANES I) collected medical and nutritional information on US residents between 1971 and 1975 (5), providing a representative sample of the entire adult, noninstitutional, civilian population of the United States with special emphasis on minority populations. The sampling procedures have been published elsewhere (6, 7).
A subsample of 6,913 adults aged 25 through 74 years who were cleared for the tests by the examining physician was given a more complete examination that included spirometry, pulmonary diffusing capacity, and an extensive medical history. All subjects completed a medical history questionnaire and were examined by a physician, who administered supplemental respiratory or cardiovascular questionnaires to subjects with positive histories and noted any positive clinical findings. The examining physicians excluded from spirometry a small proportion of subjects with very severe respiratory disease or other health conditions that would preclude performing spirometry or the inhalation of carbon monoxide. Subjects with clinical respiratory disease who could safely perform spirometry were retained in the study.

The NHANES I Epidemiologic Followup Study followed all subjects who were 25–74 years of age at the time of the baseline examination (8). Vital status was determined by tracing each subject using telephone contacts, direct mail, US Postal Service address information requests, National Death Index checks, state department of motor vehicle listings, state vital statistics files, and field visits to neighbors at last known address. By the end of the 1986 follow-up, 95 percent of the original cohort were successfully traced for a determination of their vital status, with an average duration of follow-up of 12.8 years (9). This analysis is based on subjects aged 25–74 years at the baseline examination who were successfully followed for vital event status.

### Spirometric and DL_{CO} methods

Pulmonary function measurements were made with a model 800 electronic spirometer (Ohio Medical Instruments, Inc., Cincinnati, Ohio). Each subject performed five maneuvers for each test set. The subject’s forced vital capacity was defined as the maximum forced vital capacity from at least two reproducible and error-free trials. Details of the measurement procedure and a comparison with other studies of pulmonary function level have been published elsewhere (10, 11). FEV₁ and FVC are measured in liters.

Measurements of DL_{CO} were performed with a Collins modular lung analyzer (Warren E. Collins, Inc., Braintree, Massachusetts) using a gas mixture that contained air, 10 percent helium, and 0.3 percent carbon monoxide (12). In each of three maneuvers, each subject performed a maximal inspiration of the gas mixture, held his or her breath for 10 seconds, and expired rapidly and completely to residual volume. All DL_{CO} measurements within 10 percent of the largest acceptable measurement were averaged to determine the subject’s DL_{CO}. The DL_{CO} measurement procedure has been published elsewhere (13). The measurement technique has since been standardized by the American Thoracic Society (14) and the European Respiratory Society (15), but the methods used in the NHANES I follow a similar framework. The inspired vital capacities used to calculate DL_{CO} were not available in the data set. DL_{CO} is measured in ml/min/mmHg.

### Other covariates

Cigarette smoking was assessed by a questionnaire administered by a trained interviewer, leading to a classification as never smoker, former smoker, or current smoker. Body mass index was calculated as the subject’s weight (kg)/height (m)^2. Samples of venous blood were collected and analyzed by the Centers for Disease Control for standard hematologic parameters, including serum cholesterol. Moderate alcohol consumption was defined as more than one drink each week but less than one drink each day.

### Statistical methods

The percentage of predicted pulmonary function levels was obtained for FVC, FEV₁, and DL_{CO} by dividing the observed values by the predicted values based on internal prediction equations and then multiplying the results by 100. Internal prediction equations were derived for FVC and FEV₁ based on sex-specific models for the natural logarithm of pulmonary function level as a function of race, the natural logarithms of height and age, the square of the natural logarithm of age, and an interaction between sex and the natural logarithm of height. Sex- and race-specific prediction equations for DL_{CO} were obtained from a previously published analysis of this data set (16).

The all-cause mortality hazard ratios were estimated with a Cox proportional hazard model using an S-plus function that permitted restricted cubic spline functions as well as linear functions of the predictors (17). The restricted cubic splines are a flexible approach that can detect nonlinearities in relations. Relations that appeared linear using spline models were refit as a linear function. The basic Cox model included sex, race, age, serum cholesterol, systolic blood pressure, and current smoking status. Former smoking status and the natural logarithms of pack-years smoked and current number of cigarettes smoked were not strong predictors of all-cause mortality in this data set after adjustment for age and current smoking status and did not confound the association of mortality with pulmonary function level.

Previous studies have shown a relation between all-cause mortality and standard spirometric measures.
such as the FEV₁ and peak expiratory flow rate. Since
diffusing capacity clearly varies with lung surface area
and alveolar volume, any factor associated with de-
creased alveolar volume, such as the declines in forced
vital capacity associated with age and smoking status,
will be associated with diminished diffusing capacity.
The component of DLCO that is independent of alve-
olar volume, that is, the proportion of an inhaled bolus
of carbon monoxide that is absorbed during a breath-
hold of measured duration, is the specific diffusing
capacity. To control for differences in alveolar volume
and to differentiate between diffusing capacity and
spirometry as measures of lung health, we repeated
our regression analysis using forced vital capacity as a
surrogate for alveolar volume, since more precise es-
timates of alveolar volume were not available in the
data set.

RESULTS

The initial sample of 6,913 adults selected for the
pulmonary function examination included 6,830 sub-
jects aged 25–74 years whose race was reported as
white or black (excludes 72 subjects of other races and
11 subjects of other ages). Subjects were excluded
from spirometry and DLCO measurements by the ex-
amining physician on the basis of their health history
and a physical examination. The final data set included
4,333 subjects aged 25–74 years whose race was re-
ported as white or black, consisting of 1,726 never
smokers (table 1). Their pulmonary function charac-
teristics are described in table 2.

Nonpulmonary predictors of all-cause mortality

Sex, race, age, serum cholesterol, systolic blood
pressure, and current smoking status were considered
as predictors of the all-cause mortality hazard ratio
prior to the introduction of pulmonary function vari-
able.

TABLE 1. Number of subjects and deaths by sex, clinical
respiratory disease at enrollment, and smoking status at
enrollment among 4,333 adults aged 25–74 years, First

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (no.)</td>
<td>Deaths (no.)</td>
</tr>
<tr>
<td>Total</td>
<td>2,333</td>
<td>241</td>
</tr>
<tr>
<td>With clinical respiratory disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>1,216</td>
<td>136</td>
</tr>
<tr>
<td>Former smokers</td>
<td>350</td>
<td>26</td>
</tr>
<tr>
<td>Current smokers</td>
<td>787</td>
<td>79</td>
</tr>
</tbody>
</table>

TABLE 2. Distribution of pulmonary function levels at
enrollment by sex, among 4,333 adults aged 25–74 years,
First National Health and Nutrition Examination Survey,
1971–1975

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLco (mL/min/mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forc. exp. vol. at 1 second (FEV₁) (liters)</td>
<td>Forc. exp. flow at 1 second (FEV₁) (liters)</td>
<td>Pulmonary diffusing capacity (DLco) (mL/min/mmHg)</td>
</tr>
<tr>
<td>Mean</td>
<td>Third quartile</td>
<td>3.15</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>2.53</td>
</tr>
<tr>
<td></td>
<td>First quartile</td>
<td>2.76</td>
</tr>
<tr>
<td>Mean</td>
<td>Third quartile</td>
<td>4.41</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>4.61</td>
</tr>
<tr>
<td></td>
<td>First quartile</td>
<td>3.76</td>
</tr>
</tbody>
</table>
status, body mass index, and moderate alcohol consumption. The introduction of FEV\(_1\) into the model reduced the adverse effect of black race (RR = 1.07) but did not greatly alter the effects of the other covariates. After FEV\(_1\) was introduced to the model, a 10-cm increment in height was associated with increased mortality in men (RR = 1.32, 95 percent CI 1.13–1.54), but height was not associated with mortality in women (RR = 0.93). The slope for a 1-liter decrement in FEV\(_1\) was steeper in women (RR = 1.81) than in men (RR = 1.50). This sex difference in the effect of a unit change in FEV\(_1\) disappeared when each sex was evaluated in terms of the sex-specific interquartile ranges. An interquartile change in FEV\(_1\) had the same effect on mortality in men (RR = 1.61 for a 1.18-liter decrement in FEV\(_1\)) as in women (RR = 1.63 for a 0.82-liter decrement in FEV\(_1\)). The results for FVC were similar to those for FEV\(_1\). These sex differences in the effects of FEV\(_1\) and height suggested that the model might be improved by substitution of the sex-specific percentage of predicted pulmonary function based on internal prediction equations that included height.

Sex-specific internal prediction equations were derived for pulmonary function levels of never-smoking subjects without clinical respiratory disease using logarithmic models that adjusted for race, the natural logarithms of height and age, and the square of the natural logarithm of the rate ratio (ln(RR)) was essentially linear (figure 1). The exclusion of those subjects with clinical respiratory disease at enrollment did not alter the effect of a 10 percent decrement in the percentage of predicted FEV\(_1\) and height suggested that the model might be improved by substitution of the sex-specific percentage of predicted pulmonary function levels at enrollment by sex among 4,333 adults aged 25–74 years, First National Health and Nutrition Examination Survey, 1971–1975

### Table 3. Sex-specific internal prediction equations for the natural logarithm of pulmonary function among 1,642 never smoking adults aged 25–74 years without clinical respiratory disease, First National Health and Nutrition Examination Survey, 1971–1975

<table>
<thead>
<tr>
<th></th>
<th>% of predicted forced vital capacity (% FVC)</th>
<th>% of predicted forced expiratory flow at 1 second (% FEV(_1))</th>
<th>% of predicted pulmonary diffusing capacity (% Dlco)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Third quartile</td>
<td>109.1</td>
<td>109.3</td>
<td>106.0</td>
</tr>
<tr>
<td>Mean</td>
<td>99.8</td>
<td>99.1</td>
<td>95.8</td>
</tr>
<tr>
<td>First quartile</td>
<td>89.6</td>
<td>89.2</td>
<td>85.8</td>
</tr>
<tr>
<td>Men</td>
<td>Third quartile</td>
<td>108.1</td>
<td>106.5</td>
</tr>
<tr>
<td>Mean</td>
<td>98.6</td>
<td>95.5</td>
<td>93.7</td>
</tr>
<tr>
<td>First quartile</td>
<td>89.2</td>
<td>85.8</td>
<td>82.1</td>
</tr>
</tbody>
</table>

A 10 percent decrement in the percentage of predicted FEV\(_1\) was associated with increased mortality (RR = 1.15, 95 percent CI 1.10–1.19) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. Association of the percentage of predicted FEV\(_1\) with mortality did not differ by sex (p = 0.60) or race (p = 0.70). A restricted cubic spline model revealed that association of the percentage of predicted FEV\(_1\) with the natural logarithm of the rate ratio (ln(RR)) was essentially linear (figure 1). The exclusion of those subjects with clinical respiratory disease at enrollment did not alter the effect of a 10 percent decrement in the percentage of predicted FEV\(_1\) (RR = 1.16). The effect was lower for never smokers (RR = 1.13, 95 percent CI 1.06–1.21) and current smokers (RR = 1.10, 95 percent CI 1.03–1.17) and higher for former smokers (RR = 1.23, 95 percent CI 1.15–1.32).

A 10 percent decrement in the percentage of predicted FVC also was associated with increased mor-

### Table 4. Distribution of the percentage of predicted pulmonary function levels at enrollment by sex among 4,333 adults aged 25–74 years, First National Health and Nutrition Examination Survey, 1971–1975

<table>
<thead>
<tr>
<th></th>
<th>% of predicted forced vital capacity (% FVC)</th>
<th>% of predicted forced expiratory flow at 1 second (% FEV(_1))</th>
<th>% of predicted pulmonary diffusing capacity (% Dlco)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
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<tr>
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<td>99.1</td>
<td>95.8</td>
</tr>
<tr>
<td>First quartile</td>
<td>89.6</td>
<td>89.2</td>
<td>85.8</td>
</tr>
<tr>
<td>Men</td>
<td>Third quartile</td>
<td>108.1</td>
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<tr>
<td>Mean</td>
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<tr>
<td>First quartile</td>
<td>89.2</td>
<td>85.8</td>
<td>82.1</td>
</tr>
</tbody>
</table>
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When adjusted for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index, the percentage of predicted FEV₁ was associated with increased mortality (RR = 1.15, 95 percent CI 1.10–1.20) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. However, the effect of the percentage of predicted FEV₁ on mortality could be partitioned into an effect of volume (RR = 1.14, 95 percent CI 1.09–1.19 for a 10 percent decrement in the percentage of predicted FVC) and an effect of relative flow (RR = 1.12, 95 percent CI 1.02–1.23 for a 10 percent decrement in the FEV₁/FVC ratio) in the same model.

Pulmonary diffusing capacity

A 5-ml/min/mmHg decrement in DLCO was associated with increased mortality (RR = 1.17, 95 percent CI 1.07–1.27) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. The association of DLCO with the natural logarithm of the rate ratio for all-cause mortality was significantly nonlinear (p < 0.001 for a restricted cubic spline model) with a higher rate ratio that was clearly evident for DLCO below 85 percent of the predicted value (figure 2). The shape of this empiric curve suggested that the cubic spline function could be approximated by a piecewise linear model with an arbitrary breakpoint chosen at 85 percent of that predicted.

Below 85 percent of the predicted value, each 10 percent decrement in the sex- and race-specific percentage of predicted DLCO also was associated with increased mortality (RR = 1.11, 95 percent CI 1.05–1.16) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. Association of the percentage of predicted DLCO with the natural logarithm of the rate ratio for all-cause mortality was significantly nonlinear (p < 0.001 for a restricted cubic spline model) with a higher rate ratio that was clearly evident for DLCO below 85 percent of the predicted value (figure 2). The slope for women (RR = 1.98) was higher than for men (RR = 1.49, p = 0.09). Subjects with DLCO at enrollment in the lowest decile for their sex (below 21.8 for men and 17.5 for women) had greatly increased mortality among both women (RR = 1.93, 95 percent CI 1.44–2.57) and men (RR = 1.59, 95 percent CI 1.23–2.04).

A 10 percent decrement in the sex- and race-specific percentage of predicted DLCO also was associated with increased mortality (RR = 1.11, 95 percent CI 1.05–1.16) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. Association of the percentage of predicted DLCO with the natural logarithm of the rate ratio for all-cause mortality was significantly nonlinear (p < 0.001 for a restricted cubic spline model) with a higher rate ratio that was clearly evident for DLCO below 85 percent of the predicted value (figure 2). The slope for women (RR = 1.98) was higher than for men (RR = 1.49, p = 0.09). Subjects with DLCO at enrollment in the lowest decile for their sex (below 21.8 for men and 17.5 for women) had greatly increased mortality among both women (RR = 1.93, 95 percent CI 1.44–2.57) and men (RR = 1.59, 95 percent CI 1.23–2.04).

Adjustment for either a linear or a cubic spline function of hemoglobin concentration did not alter the association. The exclusion of those subjects with clin-
ical respiratory disease at enrollment did not alter the effect of a 10 percent decrement in the percentage of predicted $D_{LCO}$ below 85 percent of the predicted value (RR = 1.32). Low $D_{LCO}$ was not simply a surrogate for current or cumulative cigarette smoking. Adjustment for linear and quadratic functions of pack-years and current cigarettes smoked per day only slightly reduced the association of all-cause mortality with the percentage of predicted $D_{LCO}$ below 85 percent of the predicted value (RR = 1.29). However, the effect was greater for former smokers (RR = 1.56, 95 percent CI 1.32–1.84) than for either current smokers (RR = 1.25, 95 percent CI 1.11–1.41) or never smokers (RR = 1.33, 95 percent CI 1.02–1.74).

Almost one quarter of the NHANES I cohort had $D_{LCO}$ measurements below 85 percent of predicted values. In this subcohort with a low percentage of predicted $D_{LCO}$, there were 223 never smokers (13 percent of all never smokers), 194 former smokers (20 percent of all former smokers), and 772 current smokers (47 percent of all current smokers). The predictors of a binary indicator of $D_{LCO}$ measurements below 85 percent of predicted values were examined among the 2,328 current and former smokers without clinical respiratory disease at enrollment. The predictors of low $D_{LCO}$ measurements were the natural logarithm of current cigarettes smoked per day (odds ratio (OR) = 2.98 for the first 20 cigarettes per day), the natural logarithm of pack-years smoked (OR = 1.78 for the first 20 pack-years), black race (OR = 1.54), and lean body mass (OR = 1.11 for a unit decrement in body mass index). Of the 223 never smokers with $D_{LCO}$ measurements below 85 percent of predicted values, 83 (37 percent) reported a spouse who smoked cigarettes. When the sample was restricted to 3,005 subjects whose FEV$_1$ was greater than 90 percent of predicted values, the percentage of predicted $D_{LCO}$ below 85 percent of the predicted value showed the same association with increased mortality (RR = 1.30 for a 10 percent decrement, 95 percent CI 1.08–1.56).

In a model with both the percentage of predicted FEV$_1$ and the percentage of predicted $D_{LCO}$ below 85 percent of predicted values, the effect of a 10 percent decrement in the percentage of predicted FEV$_1$ was unchanged (RR = 1.12, 95 percent CI 1.08–1.17), while the effect of a 10 percent decrement in the percentage of predicted $D_{LCO}$ below 85 percent of the predicted value was reduced (RR = 1.22, 95 percent CI 1.11–1.35). When the effect of the percentage of predicted FEV$_1$ was partitioned into the effects of the percentage of predicted FVC and the FEV$_1$/FVC ratio in a model with the percentage of predicted $D_{LCO}$ below 85 percent of that predicted, a 10 percent decrement in the FEV$_1$/FVC ratio was not associated with all-cause mortality among women ($p = 0.99$) and only weakly associated with mortality among men (RR = 1.09, 95 percent CI 0.98–1.22). Even for men, the model with the percentage of predicted FVC and the FEV$_1$/FVC ratio was not as predictive of all-cause mortality as the model with the percentage of predicted FEV$_1$, after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, body mass index, and the percentage of predicted $D_{LCO}$ below 85 percent of that predicted. Association of the percentage of predicted $D_{LCO}$ below 85 percent of the predicted value with mortality was unaltered by substitution of the percentage of predicted FVC and the FEV$_1$/FVC ratio for the percentage of predicted FEV$_1$ in the model.

**DISCUSSION**

In the NHANES I cohort of 4,333 men and women aged 25–74 years who were followed for an average of 12.8 years, a 1-liter decrement in FEV$_1$ was associated with increased mortality (RR = 1.59, 95 percent CI 1.38–1.83) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. In the Normative Aging Study of 1,956 men aged 21–80 years who were followed for 30 years, Weiss et al. (2) found that a 1-liter decrement in FEV$_1$ at enrollment resulted in a similar association with all-cause mortality (RR = 1.67, 95 percent CI 1.25–2.22) after adjusting for age, white cell count, serum cholesterol, systolic blood pressure, and current smoking status. Among the 2,000 men in the NHANES I cohort, the association was similar (RR = 1.61, 95 percent CI 1.36–1.90).

Based on an internal prediction equation, a 10 percent decrement in the percentage of predicted FEV$_1$ was associated with a rate ratio of 1.13 among never smokers (95 percent CI 1.06–1.21) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. In a previous analysis of the same NHANES I cohort using an external prediction equation, Bang et al. (4) reported that a 10 percent decrement in the percentage of predicted FEV$_1$ was associated with a rate ratio of 1.14 among never smokers after adjustment for sex, age, body mass index, clinical respiratory disease at enrollment, and high school graduation. The trivial difference in these two values suggests that neither the prediction equation nor the choice of model covariates is important.

For values below 85 percent of those predicted, each 10 percent decrement in the percentage of predicted...
$D_{l\text{CO}}$ was associated with increased mortality (RR = 1.33, 95 percent CI 1.21–1.45) after adjustment for sex, race, age, serum cholesterol, systolic blood pressure, current smoking status, moderate alcohol consumption, and body mass index. This association was present even for subjects without clinical respiratory disease at enrollment and for never-smoking subjects. While somewhat reduced, this association remained after controlling for the percentage of predicted FEV$_1$ or the percentage of predicted FVC and the FEV$_1$/FVC ratio. This association still remained when the sample was restricted to subjects whose FEV$_1$ levels were clinically unremarkable (an FEV$_1$ greater than 90 percent of that predicted). Hence, pulmonary diffusing capacity contains additional information about health status that is not contained in standard spirometric measurements.

The choice of a prediction model in the calculation of the percentage of predicted FEV$_1$ or the percentage of predicted $D_{l\text{CO}}$ is not a decisive factor in the analysis. We used an internal prediction equation, but other prediction equations would have performed equally well. In fact, a simple prediction equation based solely on height ($D_{l\text{CO}}$/height$^2$) had the same $t$-statistic and overall model fit for survival as the more detailed prediction equation. Hence, the predictive power of the percentage of predicted $D_{l\text{CO}}$ for survival is not dependent on the specific nature of our prediction equation for $D_{l\text{CO}}$.

These findings are biologically plausible. The standard spirometric measurements (FVC, FEV$_1$, and the FEV$_1$/FVC ratio) primarily describe the ability to mechanically exchange air. Controlling for those factors, $D_{l\text{CO}}$ provides information about the ability of the alveolar region to diffuse gases and the effective perfusion of the alveolar surface. We have previously shown that cigarette smoking provides larger and earlier effects on $D_{l\text{CO}}$ than on FVC (12). Thus, in the current study of pulmonary function as a predictor of life expectancy, $D_{l\text{CO}}$ measured at enrollment may serve as a better indicator of the initial damage due to cigarette smoke and other environmental factors than FVC or FEV$_1$. While active cigarette smoking is a risk factor among current and former smokers, the association between $D_{l\text{CO}}$ and mortality among never-smokers suggests that other environmental factors such as environmental tobacco smoke play a substantial role.

Damage to the alveolar region can occur with little effect on FEV$_1$ such as occurs in the early stages of pulmonary interstitial diseases. Isolated $D_{l\text{CO}}$ deficits can be seen in the early stages of interstitial pulmonary fibrosis, even with normal vital capacity (18), and can occur before the disease is clinically manifest. In patients with isolated $D_{l\text{CO}}$ reduction and normal FEV$_1$ and FVC, the flows and the FEV$_1$/FVC ratio are unusually high and reflect increased elastic recoil (19). Normal subjects have considerable reserve diffusing capacity above the minimum required to fully saturate the pulmonary blood circulation, and all-cause mortality was not associated with increments of the percentage of predicted $D_{l\text{CO}}$ for the 73 percent of our subjects with the percentage of predicted $D_{l\text{CO}}$ levels above 85 percent of predicted values. For the 27 percent of our subjects with the percentage of predicted $D_{l\text{CO}}$ levels below 85 percent of predicted values, decrements in the percentage of predicted $D_{l\text{CO}}$ levels were linearly associated with increased all-cause mortality even after adjustment for spirometric measures.

These results indicate that decrements in pulmonary function (RR = 1.15 for a 10 percent decrement in the percentage of predicted FEV$_1$) or diffusing capacity (RR = 1.33 for a 10 percent decrement in the percentage of predicted $D_{l\text{CO}}$ below 85 percent of that predicted) are as important a determinant of all-cause mortality as increments in serum cholesterol (RR = 1.05 for a 30-mg/dl increment) and systolic blood pressure (RR = 1.14 for a 15-mmHg increment). These results indicate that pulmonary diffusing capacity plays a role in all-cause mortality within the general US population independent of standard spirometry measures and even in the absence of apparent clinical respiratory disease.

ACKNOWLEDGMENTS

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