LONGITUDINAL AND CROSS-SECTIONAL ESTIMATES OF PULMONARY FUNCTION DECLINE IN NEVER-SMOKING ADULTS

JAMES H. WARE, DOUGLAS W. DOCKERY, THOMAS A. LOUIS, XIPING XU, BENJAMIN G. FERRIS, JR., AND FRANK E. SPEIZER


This paper describes methods for simultaneous cross-sectional and longitudinal analysis of repeated measurements obtained in cohort studies with regular examination schedules, then uses these methods to describe age-related changes in pulmonary function level among nonsmoking participants in the Six Cities Study, a longitudinal study of air pollution and respiratory health conducted between 1974 and 1983 in Watertown, Massachusetts; Kingston and Harriman, Tennessee; St. Louis, Missouri; Steubenville, Ohio; Portage, Wisconsin; and Topeka, Kansas. The subjects, initially aged 25–74, were examined on three occasions at 3-year intervals. Individual rates of loss increased more rapidly with age than predicted from the cross-sectional model. For example, for a male of height 1.75 m, the cross-sectional model predicted an increase in the annual rate of loss of FEV₁ from 23.7 ml/yr at age 25 to 39.0 ml/yr at age 75, while the longitudinal model gave rates of loss increasing from 12.9 ml/yr at age 25 to 58.2 ml/yr at age 75. These results contrast with those of other studies comparing longitudinal and cross-sectional estimates of pulmonary function loss.

cross-sectional studies; longitudinal studies; lung; models, statistical; respiratory function tests; spirometry

Longitudinal studies are now widely used to characterize age-related changes in physiologic parameters and determinants of rate of change (1). Despite an extensive statistical literature on methods for analyzing longitudinal data, however, the various methods used to analyze epidemiologic data have proved to be difficult to interpret and compare (2). There is a continuing need for statistical methods that correspond to natural ways of describing longitudinal data, especially individual rates of change, and that provide graphical and tabular data summaries for evaluation of the adequacy of the proposed models.

Longitudinal studies of an initial cross-sectional sample provide the opportunity to compare longitudinal and cross-sectional

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Abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.
1 Department of Biostatistics, Harvard School of Public Health, Boston, MA.
2 Department of Environmental Science and Physiology, Harvard School of Public Health, Boston, MA.
3 The Channing Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.
4 Division of Biostatistics, University of Minnesota School of Public Health, Minneapolis, MN.
Reprint requests to Dr. Douglas W. Dockery, Department of Environmental Science and Physiology, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115.
Supported in part by National Institute of Environmental Health Sciences Grant ES-01108 and ES-0002, Environmental Protection Agency Cooperative Agreement CR-811650 and Electric Power Research Institute Contract RP-1001. Dr. Dockery was supported by a Mellon Foundation Faculty Development Award.
estimates of rate of change of physiologic variables during childhood and adult life. This comparison is of interest because it sheds light on cohort effects in cross-sectional data and provides the opportunity to evaluate cross-sectional studies of longitudinal questions. Two recent publications (3, 4) used different statistical methods to compare cross-sectional and longitudinal estimates of rates of pulmonary function loss during adulthood. Both concluded that individual rates of loss are smaller than would be predicted from cross-sectional data.

This paper describes methods for simultaneously modeling cross-sectional and longitudinal information in longitudinal studies and uses these methods to compare cross-sectional and longitudinal estimates of age-related loss of forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) during adult life. The methods can be viewed as an application of the methods proposed by Liang and Zeger (5), in that they re-express the repeated observations of the dependent variable as the initial value and the changes in response between successive examinations. The successive differences, the natural measures of change, can then be analyzed by ordinary least squares regression, with a modified variance to correct for dependence among observations, or can be analyzed by autoregressive methods. Both methods are used in this report. Analyses of data collected as part of the Six Cities Study of Air Pollution and Health (6, 7) show that individual rates of loss accelerate more rapidly with age than predicted by the cross-sectional model. Individual rates of loss are greater than the cross-sectional model would predict after about age 50 years. This result differs from that obtained in the two previously cited investigations.

**Materials and methods**

**Study population**

The study population consisted of a random sample of adults aged 25–74 years selected from census lists in each of six cities in the eastern and midwestern United States (Watertown, Massachusetts; Kingston-Harriman, Tennessee; Steubenville, Ohio; a geographically defined portion of St. Louis, Missouri; Topeka, Kansas; and Portage, Wisconsin). Participants were enrolled over a 3-year period beginning in September 1974 and invited to come to a central office to complete a standardized respiratory disease questionnaire and to perform a forced expiratory maneuver with a water-filled 8-liter recording survey spirometer (Warren E. Collins, Braintree, Massachusetts). Those not attending the central office were seen in their homes. Details of testing procedures have been described elsewhere (7). FEV$_1$ was determined by back-extrapolation and optimal values of FEV$_1$ and FVC (corrected to body temperature, pressure, and saturation with water vapor) were determined for each examination. Each participant was invited back for a follow-up examination at the same time of year 3 years after the first examination and again 6 years after the initial examination. Each follow-up examination included administration of a standardized respiratory disease questionnaire and a pulmonary function examination using the same methods and spirometers. For this analysis, the sample was restricted to white subjects who reported never having smoked, who reported no respiratory symptoms, and who provided acceptable pulmonary function tracings. If a subject initially classified as a nonsmoker reported having begun smoking during the study, all observations after smoking began were eliminated from this analysis.

Results from cross-sectional analysis of pulmonary function measurements at the first examination have been reported elsewhere (7). For this report, several changes were made in the data used in the earlier cross-sectional analysis to ensure that the data gathered at the three examinations were internally consistent. First, the spirometric tracings in the first city studied, Watertown, Massachusetts, had been read
by a method different from that used subsequently. For this study, those tracings were remeasured by standard methods. The remeasured \( \text{FEV}_1 \) values were increased by an average of 4.2 ml relative to the initial values. Second, the \( \text{FEV}_1 \) and \( \text{FVC} \) values in Steubenville, Ohio, had been obtained from a modified spirometric examination protocol designed to investigate the effects of an increase in the required number of acceptable blows on the pulmonary function values (8). The modified protocol required five rather than three acceptable blows for each participant. In the earlier cross-sectional analysis (7), we defined \( \text{FEV}_1 \) and \( \text{FVC} \) for these examinations as the mean of the best three among five acceptable tracings. For this report, \( \text{FEV}_1 \) and \( \text{FVC} \) were recalculated as the mean value obtained from the first three acceptable blows. This recalculation decreased the \( \text{FEV}_1 \) and \( \text{FVC} \) values by an average of 35.7 ml and 31.5 ml, respectively. Finally, the repeated measurements of height were reviewed to identify intervals in which height changes differed by more than four standard deviations from the population mean height change. Original records were reviewed for these cases and corrections made when appropriate. Other values identified as outliers were replaced by the modal measurement of height for that individual, except when the record for the examination noted arthritis, stooping, or surgical procedures. For 11 subjects with only two examinations and inconsistent height values, the second examination was deleted from the analysis.

**Statistical methods**

Previously reported cross-sectional analyses of the data from the initial pulmonary function examinations of this cohort showed that \( \text{FEV}_1 \) and \( \text{FVC} \) measurements can be corrected for body size by dividing by the square of height (7). These adjusted values were used in all analyses, and results were converted back to volume units by multiplying predicted values by the square of the subject’s height. Representative conversions, using a height of 1.75 m for males and 1.61 m for females (the mean heights in the sample), are used to illustrate the effects of height correction. To avoid spurious variability between occasions due to errors in the measurement of height, the initial longitudinal analyses of \( \text{FEV}_1 \) and \( \text{FVC} \) reported in this paper use a single value, the height at the first examination, to adjust all measurements for a given individual. In a separate analysis, we investigate age-related changes in height observed and quantify the contribution of loss of height with age to differences in the cross-sectional and longitudinal results.

Two closely related statistical methods were used to analyze the data. For both methods, the observations at the three examinations were transformed to three new variables, the initial observation, \( \text{PF}_{it} \), and the two values of change in pulmonary function level between successive examinations,

\[
D_{i1} = \text{PF}_{i2} - \text{PF}_{i1}
\]

and

\[
D_{i2} = \text{PF}_{i3} - \text{PF}_{i2},
\]

where \( \text{PF}_{it} \) represents the measurement of either \( \text{FEV}_1/\text{Ht}^2 \) or \( \text{FVC}/\text{Ht}^2 \) for subject \( i \) at visit \( t \).

In Method 1, called here the first difference method, the initial observations and differences were analyzed by ordinary least squares. The height-adjusted values from the initial examination were fitted by sex-specific cross-sectional models of the form

\[
\text{PF}_{it} = b_0 + b_1 \ast (\text{Age}_{it}) + b_2 \ast (\text{Age}_{it})^2,
\]

where \( \text{Age}_{it} = \text{Age}_{i} - 50 \) (6). To fit the pooled data, this model was augmented by adding an indicator variable for sex.

Individual participants provided up to two measurements of pulmonary function change during 6-year follow-up. These changes were fitted to a sex-specific linear
model of the form
\[ D_t = b_i^*(\text{Age}_{i,t+1} - \text{Age}_{i,t}) + b_{ij}^*(\text{Age}_{i,t+1} - \text{Age}_{i,t}) \] (2)
by ordinary least squares. This analysis provided estimates of the linear and quadratic effects of age on pulmonary function loss which were directly comparable to the coefficients of the cross-sectional model.

This method provides estimates of cross-sectional and longitudinal parameters that are unbiased if data are missing completely at random (9). Because the initial values and successive differences for individual subjects are statistically dependent, however, it does not provide valid estimates of their standard errors. Consistent estimates of the variances of the ordinary least squares estimates were calculated using methods for robust estimation of variances (5). The robust and ordinary least squares estimates of the standard errors of the longitudinal coefficients are compared in this report.

This noniterative procedure is easy to implement and provides a natural description of individual changes between successive examinations. It is, however, potentially less efficient and more sensitive to bias from missing observations than methods that model the covariances among the initial values and successive differences. If the vectors of individual observations have a first-order autoregressive error structure, maximum likelihood estimates can be obtained by a simple modification of the noniterative analysis. For the first order autoregressive analysis, the cross-sectional model (equation 1) is not changed, but the longitudinal model (equation 2) becomes

\[ D_t = b_i^*(\text{Age}_{i,t+1} - \text{Age}_{i,t}) + b_{ij}^*(\text{Age}_{i,t+1} - \text{Age}_{i,t}) + b_{ij}^*(\text{PF}_t - E(\text{PF}_t)), \]

where \( E(\text{PF}_t) \) is the expected value of \( \text{PF}_t \). The parameter estimates for this model were obtained by an iterative algorithm which successfully updated the regression coefficients and the variance parameters.

Standard errors for these estimates were also estimated robustly (5).

The initial analyses of the height and pulmonary function measurements were used to identify observations or differences with standardized residuals of 4 or more. These observations were verified or corrected from original records. The analysis was then repeated without the remaining observations having standardized residuals in excess of 4 to ensure that these potential outliers did not have a large influence on the results.

A random sample of 8,842 adults aged 25–74 years was selected and examined in six US cities between 1974 and 1977. These subjects were re-examined twice at 3-year intervals. This report is based on data from the 2,454 white subjects who reported at every examination that they had never smoked and who had acceptable FEV1 and FVC measurements at the initial examination (table 1). Of these, 1,973 (80 percent) were re-examined 3 years after their initial examination, and 1,713 (70 percent) after 6 years.

RESULTS

Mean FEV1 at the initial examination is given by sex and 5-year interval of initial age in table 2. Table 3 gives the average annual rate of loss of FEV1 during 3-year follow-up intervals, again by sex and half-decade of age at the beginning of the interval. The mean rates of loss are negative for all age groups and increase in absolute value with age.

### Table 1

<table>
<thead>
<tr>
<th>Numbers of asymptomatic never-smokers with acceptable spirometric examinations at the initial and follow-up visits: Six Cities Study of Air Pollution and Health, 1974–1983</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of men</td>
</tr>
<tr>
<td>Initial</td>
</tr>
<tr>
<td>First follow-up</td>
</tr>
<tr>
<td>Second follow-up</td>
</tr>
</tbody>
</table>
Longitudinal and cross-sectional estimates of rates of loss

Cross-sectional and longitudinal coefficients for the linear (age) and quadratic age (age²) effects of aging on FEV₁/Ht² were estimated using the first difference and first order autoregressive models and estimation procedures described in Materials and Methods (table 4). Because age was centered at 50 years, the intercept is an estimate of the mean value of FEV₁/Ht² for a 50-year-old subject. The coefficients of (Age – 50) give the estimated annual rates of decline of the FEV₁/Ht² ratio for a 50-year-old subject. For a 25-year-old man whose height at the initial examination was 1.75 m, the first difference model gives a cross-sectional estimate of FEV₁ loss during the subsequent year of

\[-[(−24 +25)∗(10.20)] + (24² −25²)∗(0.050)]∗(1.75²) = −23.7 ml,

where 50 has been subtracted from each age to reflect the centering used in model fitting. Similarly, the longitudinal estimate from the first difference model is

\[-[(−24 +25)∗(11.46)] + (24² −25²)∗(0.148)]∗(1.75²) = −12.9 ml.

For a 75-year-old male of the same height, the longitudinal estimate

\[-[(−24 +25)∗(0.148)]∗(1.75²) = −12.9 ml.

\[-[(−24 +25)∗(11.46)] + (24² −25²)∗(0.148)]∗(1.75²) = −12.9 ml.

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For a 75-year-old male of the same height, the longitudinal estimate
TABLE 4
Cross-sectional and longitudinal estimates of age-related changes in FEV1/Ht2: Six Cities Study of Air Pollution and Health

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept (ml/m²)</th>
<th>(Age - 50) (ml/m²/yr)</th>
<th>(Age - 50)² (ml/m²/yr²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First difference model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,183.9 (10.1)*</td>
<td>-10.20 (0.49)</td>
<td>-0.050 (0.036)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-11.46 (0.82)</td>
<td>-0.148 (0.033)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>979.0 (4.6)</td>
<td>-10.06 (0.23)</td>
<td>-0.061 (0.017)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-10.41 (0.39)</td>
<td>-0.118 (0.014)</td>
</tr>
<tr>
<td><strong>First order autoregressive model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,183.0 (9.6)</td>
<td>-10.14 (0.50)</td>
<td>-0.044 (0.035)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-11.35 (0.80)</td>
<td>-0.143 (0.032)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>976.9 (4.4)</td>
<td>-10.03 (0.23)</td>
<td>-0.049 (0.016)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-10.20 (0.39)</td>
<td>-0.115 (0.014)</td>
</tr>
</tbody>
</table>

* Standard error, by robust methods, in parentheses.

As would be expected, the first order autoregressive model gives almost identical results. For example, the cross-sectional and longitudinal estimates of annual change for a 25-year-old man of height 1.75 m are -24.5 ml and -13.3 ml, respectively. In subsequent tables, we report only the results for the first-order autoregressive model.

The cross-sectional and longitudinal estimates of rate of change were compared to observed rates of change within each age interval (figures 1, 2). The observed changes are the mean values of the annual rates of loss for observations grouped by 5-year intervals age at the beginning of the interval (table 3). Both the cross-sectional and longitudinal estimates of annual loss of FEV1 increase with age. As noted previously, individual rates of loss accelerate more rapidly with increasing age than predicted by the cross-sectional model. By age 75, average annual rates of loss are almost twice as large as the cross-sectional estimates. The most striking feature of these figures is the close agreement between longitudinal estimates and observed mean rates of change within age intervals (see also table 3). The cross-sectional model over- and underestimates mean rates of loss at younger and older ages, respectively, but does provide good fit to the cross-sectional data on age and FEV1 from the initial examination (table 2).

The standard errors and tests of significance for the first difference model were based on the robust methods described previously (see Materials and Methods). The differences between the robust and ordinary least squares estimates of standard errors were small. For men, for example, ordinary least squares regression gave standard errors of 0.981 and 0.035 for the longitudinal parameters, corresponding to 119
Figure 1. Comparison of predicted and observed rates of change of FEV₁ for male study participants: Six Cities Study of Air Pollution and Health, 1974–1983. The circles and error bars represent the mean ± standard error of the observed annual rate of loss of FEV₁, for subjects grouped by 5-year age interval. The solid line connects the means of the predicted rates of loss calculated from the cross-sectional model and the dashed line connects the predicted means from the longitudinal model.

Examination effects

Although the same procedures were used at all three examinations, the age-adjusted mean rate of loss in pulmonary function was somewhat greater in the second than...
in the first interval. When the longitudinal model was refitted with an indicator variable for the first interval, the estimated difference in the age-adjusted annual mean rate of loss in the two intervals was 11.0 ml/yr (standard error (SE) = 6.7 ml/yr) for a man 1.75 m tall and 10.6 ml/yr (SE = 2.6 ml/yr) for a woman of height 1.61 m (table 6). When the data were examined separately for each city, examination effects of very similar size were found in all six cities. These consistent differences suggest some systematic examination effects, such as learning or changes in equipment or examination procedures. The latter two possibilities were explored but could not be shown to have been present. The inclusion of an examination effect in the model had a negligible effect on the quadratic terms in the cross-sectional and longitudinal models (table 6). Thus, adjustment for an examination effect did not alter the finding of more rapid acceleration in rate of loss with age than predicted by the cross-sectional model.

**Effects of height loss on the comparison of longitudinal and cross-sectional estimates**

The results presented in tables 4–6 contain a subtle effect due to differences in the treatment of height in the cross-sectional and longitudinal analyses. The longitudinal...
Table 5
Cross-sectional and longitudinal estimates of age-related changes in FVC/Ht²: Six Cities Study of Air Pollution and Health

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept (ml/m²)</th>
<th>(Age - 50) (ml/m²/yr)</th>
<th>(Age - 50)² (ml/m²/yr²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,470.8 (11.3)*</td>
<td>-10.32 (0.57)</td>
<td>-0.003 (0.043)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-12.92 (0.84)</td>
<td>-0.246 (0.032)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,208.4 (5.4)</td>
<td>-9.85 (0.27)</td>
<td>-0.106 (0.019)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-11.33 (0.43)</td>
<td>-0.170 (0.016)</td>
</tr>
</tbody>
</table>

* Standard error, by robust methods, in parentheses.

Table 6
Cross-sectional and longitudinal estimates of age-related changes in FEV₁/Ht² when an examination effect is included in the model: Six Cities Study of Air Pollution and Health

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept (ml/m²)</th>
<th>(Age - 50) (ml/m²/yr)</th>
<th>(Age - 50)² (ml/m²/yr²)</th>
<th>Exam (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,182.7 (9.7)*</td>
<td>-10.17 (0.50)</td>
<td>-0.044 (0.035)</td>
<td>3.6 (2.2)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-9.61 (1.48)</td>
<td>-0.137 (0.032)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>976.7 (4.4)</td>
<td>-10.06 (0.23)</td>
<td>-0.050 (0.016)</td>
<td>4.1 (1.0)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-8.32 (0.63)</td>
<td>-0.108 (0.014)</td>
<td></td>
</tr>
</tbody>
</table>

* Standard error, by robust methods, in parentheses.

Analyses used a single height value for all examinations. This reduced variability due to errors in the measurement of height but also eliminated any losses in measured height associated with aging. The cross-sectional estimates of pulmonary function decline were influenced by age-related height loss, however, because only one height measurement was available at the age of examination. To explore this issue, we fitted cross-sectional and longitudinal models for height measurements at the three examinations as a quadratic function of age.

Both the longitudinal and cross-sectional analyses showed age-related loss of height (table 7, figures 3, 4). For men, the longitudinal model gave a predicted height loss of 3.0 cm from age 25 to 75, with most of the loss occurring after age 50 (table 7). This value represents the tendency of individuals to experience declines in measured height as they age. The cross-sectional model gave a predicted loss of 7.0 cm over the same 50-year interval. This represents the combined effects of aging and differences among cohorts. Thus, we estimate that approximately half of the association between height and age observed at the initial examination is due to aging.

The oldest group of men had a mean rate of height loss of almost 0.5 cm/yr (figure 3). This mean was based on the data for 13 men. Each of these height changes was checked against the original data and no errors were identified. Because this group was small, deletion of these 13 values had a negligible effect on the longitudinal model. These values highlight the fact, however, that substantial height losses sometimes occur in elderly subjects.

In an idealized situation, one would record the height of each person in young adulthood, say age 25, and use this value to...
TABLE 7
Cross-sectional and longitudinal estimates of age-related changes in height: Six Cities Study of Air Pollution and Health

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept (cm)</th>
<th>(Age - 50) (cm/yr)</th>
<th>(Age - 50)^2 (cm/yr^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>175.0 (4.1)*</td>
<td>-0.14 (0.02)</td>
<td>-8.11 x 10^{-4} (1.5 x 10^{-3})</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>-0.06 (0.01)</td>
<td></td>
<td>-2.16 x 10^{-2} (4.1 x 10^{-4})</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>161.4 (2.1)</td>
<td>-0.09 (0.01)</td>
<td>-3.00 x 10^{-3} (7.6 x 10^{-4})</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>-0.08 (0.01)</td>
<td></td>
<td>-2.62 x 10^{-3} (2.7 x 10^{-4})</td>
</tr>
</tbody>
</table>

* Standard error, by robust methods, in parentheses.

FIGURE 3. Comparison of predicted and observed rates of change of height for male study participants: Six Cities Study of Air Pollution and Health, 1974–1983. The circles and error bars represent the mean ± standard error of the observed annual rate of loss of height for subjects grouped by 5-year age interval. The solid line connects the means of the predicted rates of loss calculated from the cross-sectional model and the dashed line connects the predicted means from the longitudinal model.

normalize all subsequent measurements of FEV\textsubscript{1}. This would avoid the blunting of loss in pulmonary function resulting from correction by a declining denominator (height\textsuperscript{2}). To mimic this approach, we used the longitudinal model for height loss to calculate a predicted height at age 25 for each individual based on the height at the
initial examination, normalized all values of FEV₁ by the square of this value, and repeated the cross-sectional and longitudinal analysis. This analysis showed a smaller discrepancy between the cross-sectional and longitudinal estimates of age-related loss than obtained initially (table 8), but the differences remained statistically significant in women and in the pooled analysis ($\chi^2 = 7.48$, 2 df, $p < 0.05$ for the pooled data, $\chi^2 = 2.47$, $p = 0.39$ for men, $\chi^2 = 6.03$, $p < 0.05$ for women).

**DISCUSSION**

As Buist (10) has noted, previous studies have obtained remarkably consistent cross-sectional and longitudinal estimates of average rate of change of FEV₁ during adult life. In this study, the cross-sectional and longitudinal estimates of average rates of loss were very similar at age 50, the middle of the age range. Because the initial ages were evenly distributed from 25 to 75, the cross-sectional and longitudinal estimates of the average rate of loss for the entire sample were also quite similar. The longitudinal data, however, showed a much larger acceleration of the rate of loss with age than predicted from the cross-sectional model. Thus, the cross-sectional estimates were higher than the observed rates of loss for subjects less than about age.
Cross-sectional and longitudinal estimates of age-related changes in FEVi/Ht² using predicted height at age 25: Six Cities Study of Air Pollution and Health

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept (ml/m²)</th>
<th>(Age - 50) (ml/m²/yr)</th>
<th>(Age - 50)² (ml/m²/yr²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>1,180.9 (9.6)*</td>
<td>-10.81 (0.49)</td>
<td>-0.065 (0.035)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-11.26 (0.81)</td>
<td>-0.138 (0.032)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>971.9 (4.4)</td>
<td>-10.79 (0.22)</td>
<td>-0.066 (0.016)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>-10.10 (0.38)</td>
<td>-0.108 (0.014)</td>
</tr>
</tbody>
</table>

* Standard error, by robust methods, in parentheses.

50, and too low for older subjects (figures 1 and 2).

Although we found that the longitudinal estimate of rate of loss increases more rapidly with age than the cross-sectional estimate, other investigators (3, 4) have reported the opposite result. In subsequent paragraphs, we investigate possible explanations for this discrepancy and for the difference between cross-sectional estimates and observed rates of change.

Model misspecification

Figures 1 and 2 show that the longitudinal models described in this report provide excellent fit to the observed rates of change of pulmonary function. Rates of loss of both FEVi and FVC show a clear acceleration with age in these data and in other studies (11, 12). The data also indicate that the rate of loss increases linearly with age between ages 25 and 75, implying a quadratic relation between age and pulmonary function level. Prediction models that are linear in age (3) imply a constant annual rate of loss of pulmonary function for all ages and will fail to describe this acceleration. The same results were obtained when the sample was restricted to examinations before age 70, and both before and after age 50, indicating that this pattern is not age-specific.

The longitudinal model used in this study was consistent with the cross-sectional model, in that the longitudinal model could be obtained by differencing the cross-sectional model at successive ages. Thus, the coefficients of age and the square of age in the two models were directly comparable. Other investigators (4) have compared models that did not have this property, raising the possibility that the cross-sectional and longitudinal estimates of rates of loss were not truly comparable. Glindmeyer et al. (3) reported data for only 52 subjects, and their linear models did not allow for the acceleration of rate of loss with age. The large data set available for our study makes it possible to exclude sampling variation as an explanation for the results.

In previous work (6), we demonstrated that pulmonary function level is proportional to the square of standing height. Longitudinal estimates of rate of loss were insensitive to the choice of normalization for height, because individual changes in height were small relative to between-subject variation in height. The cross-sectional results were sensitive to the assumed form of the height association, however, because height was strongly associated with age in the cross-sectional data. Thus, misspecification of the normalization for height could affect the comparison between longitudinal and cross-sectional estimates of age-specific loss of pulmonary function. This issue is discussed later under cohort effects.

A similar issue arises in the model for age. Louis et al. (13) showed that when the model for age is specified incorrectly the estimated annual rate of loss will depend
on the age distribution of the sample. Becklake and Permutt (14) observed this bias in reviewing various cross-sectional studies. Our model for the effects of age and height on pulmonary function gave excellent fit to the observed cross-sectional and longitudinal data, so the differences we observe cannot be attributed to model misspecification.

Selection effects

Some previous comparisons of cross-sectional and longitudinal data restricted the analysis to subjects with complete data (3). Because mortality and loss to follow-up are associated with low pulmonary function level (15–17), including only those subjects with complete data in the cross-sectional analysis will produce positive bias in the mean response. Because rates of mortality and loss to follow-up are greater in the older subjects, this bias will be larger in older participants, producing reduced cross-sectional estimates of rate of loss. A reanalysis of the data for subjects with complete data showed, however, that this bias is small in this study.

Even when subjects with incomplete data are included in the analysis, selection effects can occur. Cross-sectional estimates of age effects will be biased if the initial sample is not representative of the population or if pulmonary function level is a predictor of loss to follow-up. Observations may be lost through death, failure to participate in a subsequent examination, or by a failure to obtain an acceptable pulmonary function measurement.

Initial selection of subjects for the Six Cities Study was based on random sampling in each community, but not all individuals selected agreed to participate in the initial examination. This problem arises in most population-based studies, and quantification of the selection effects induced by nonparticipation would require a sub-study of the nonparticipants population.

Unacceptable pulmonary function tests have been shown to be associated with increased symptoms and higher mortality (17). Failure to provide an acceptable pulmonary function test has also been shown to be associated with a faster rate of decline (16). Thus, selection effects are present in the cross-sectional analysis. Selection effects will also arise in the longitudinal analysis if rate of pulmonary function loss during an interval is a predictor of return for reexamination. This selection effect also could be quantified only by examining a subset of those who did not return. It is likely that level of pulmonary function is more important than rate of decline as a risk factor for death or incapacitating illness.

Statistical theory is now available to describe the conditions under which missing data will cause bias in estimates of regression coefficients (9). Models based on the correct joint distribution of the repeated observations will provide unbiased estimates of the regression coefficients if the data are missing at random; that is, if the probability of a missing observation does not depend on the unobserved data values. The generalized estimating equation methods proposed by Liang and Zeger (5) require a stronger assumption, that the data are missing completely at random. The practical importance of this distinction may be limited, however, because 1) situations in which the data are missing at random but not completely at random may be rare, 2) the assumption that the data are missing at random cannot be tested, and 3) probability models are always approximations to the true joint distribution. Thus, we have no reservations about using the methods of Liang and Zeger in this setting.

In our data, the estimated first-order correlation between successive observations varied between 0.86 and 0.89. For an autocorrelation of 0.88, for example, the first-order autoregressive analysis can be viewed as an ordinary least squares regression analysis of the values $PF_1$, $PF_2 - 0.88PF_1$, and $PF_3 - 0.88PF_2$. Thus, the first-difference and autoregressive models are
closely related. In this situation, the first-difference model is attractive because of its conceptual and computational simplicity. To allow for possible heterogeneity of variance and misspecification of the covariance structure in the data, variances of estimates obtained by both methods were estimated robustly.

**Period effects**

Changes in techniques or instruments can produce period effects, that is, differences in pulmonary function measurements between examinations, which bias the observed change in FEV\textsubscript{1} or FVC. An analysis of variance showed a statistically significant difference between spirometers used in this study. The range of these differences was $-1.5$ percent to $+1.4$ percent. However, because the same spirometers were used with only small modifications throughout the study and because of the essentially random allocation of spirometers to subjects, spirometer effects should not be a source of bias.

Differences in administration of the spirometric examination can also produce bias, both longitudinally and cross-sectionally. In the Six Cities Study, spirometric examinations were supervised and, in many cases, administered by a team of field supervisors that visited all six cities. Procedures were carefully standardized and periodically reviewed. An ancillary study of methods in Steubenville, Ohio did produce a difference in spirometric procedures (8), but this difference has been eliminated for this analysis. Thus, differences in spirometric procedures should have a minimal impact on these analyses.

Other investigators have observed improved performance at second and later examinations, possibly due to "learning" effects (3, 4). Analysis of the cross-sectional residuals in our data set showed that FEV\textsubscript{1} measurements at the first examination were lower than expected based on values at the two subsequent examinations (3 and 6 years later) by $33.0 \pm 20.1$ ml for men and $31.8 \pm 7.8$ ml for women. City-specific analyses showed this effect to be present in all six cities, with no significant difference between the cities. Thus, learning effects are a plausible explanation for the observed examination effects.

When values of FEV\textsubscript{1} at the initial examination were increased by these amounts, the longitudinal estimate of annual change for a 50-year-old male became 41.0 ml/year, compared with 31.2 ml/year without the adjustment. For a 50-year-old female, the longitudinal estimate of annual change became 32.7 ml/year, compared with 27.0 ml/year. For both sexes, the effect on the estimate of the quadratic coefficient for age was negligible. The learning effect was independent of age and therefore did not affect the cross-sectional estimates of annual decline, which were based only on the initial observation. Thus, examination effects, possibly due to learning, do not explain the observation that individual rates of loss accelerate more rapidly than predicted from the cross-sectional model.

Glindmeyer et al. (3) also observed that FEV\textsubscript{1} and FVC measurements at the first of five annual visits were lower than would be expected from the subsequent four measurements. In that study, deletion of the first measurements increased the estimated rate of loss of FEV\textsubscript{1} by 40 percent, and the estimated annual loss of FVC by 140 percent.

Burrows et al. (4) reported variation in mean FEV\textsubscript{1} over eight examinations which they estimated to be less than 37 ml at any specific examination. Fletcher et al. (18) also found such survey-specific differences. Thus, currently accepted methods for standardizing pulmonary function measurements do not prevent variability of the order of 1 percent or less in mean pulmonary function level between examinations.

Period effects will bias the longitudinal estimates of annual loss, but not the cross-sectional estimates. Unless there are age-specific differences in such period effects, the effect should be constant across ages.
PULMONARY FUNCTION DECLINE IN ADULTS

Cohort effects

Cohort effects arise from systematic differences in the study population that are associated with age at enrollment. For example, the cross-sectional model implicitly assumes that differences between 75-year-old and 25-year-old subjects are due to aging rather than underlying differences between the two age groups. Cohort effects will bias the cross-sectional estimates of rate of loss but will not affect longitudinal estimates derived from repeated measurements on the same subjects.

Glindmeyer et al. (3) suggest that the difference they observed between cross-sectionally and longitudinally determined rates of loss of pulmonary function was due to cohort effects. In particular, they suggest that the form of the relation between pulmonary function and height has changed over time, as suggested by the temporal increase in height-specific pulmonary function values. They also suggest that higher respiratory illness rates and greater environmental and occupational exposures encountered when today’s older subjects were young may have accelerated their loss of pulmonary function. Such cohort effects could produce cross-sectional estimates of rate of loss that exceed individual rates of loss, as reported by Glindmeyer et al. (3) and as also reported by Burrow et al. (4) for older participants.

In the Six Cities data, we obtained the opposite result. Individual rates of decline were greater among older subjects than predicted by the cross-sectional model. We attribute part of this difference to temporal changes in height—both secular changes in the population, a cohort effect, and longitudinal changes in individuals, a period effect—but this effect does not provide a complete explanation, especially for FVC.

Ultimately, however, we find it difficult to explain the inconsistencies between our findings and those of other investigators. Glindmeyer et al. (3) reported data for only 52 subjects, so that the difference may be due in part to sampling variability in their data. Burrows et al. (4) had a larger sample of healthy nonsmokers but reported results from a variety of models and did not demonstrate agreement between the fitted models and the data. Thus, they do not show that the reported difference between longitudinal and cross-sectional results is found in the data as well as the regression models.

Given the size of our data set and the close agreement between data and fitted models, we believe that this analysis provides compelling evidence that older healthy nonsmokers lose pulmonary function at a more rapid rate than cross-sectional analysis would predict. Intuitively, this is most likely to be due to the effects of substantial attrition of older subjects with low pulmonary function levels on the cross-sectional analysis.

The longitudinal methods described in this report will provide a framework for investigating the effects of other risk factors, including personal cigarette smoking, passive smoking, and outdoor air pollution, in the larger cohort from which this sample of nonsmokers was drawn. The method is attractive for both epidemiologic and clinical use, because the pulmonary function change and the relevant covariates can be calculated from data obtained at two successive visits. Although we have limited this discussion to studies with regular examination schedules, the method can be extended to studies with irregular examination schedules. Some caution is indicated in applying this method, however, because it may be somewhat more sensitive to data-dependent attrition than maximum likelihood methods. This will be less of a concern in our data than in other settings because the high correlations between successive observations produce a close correspondence between the first-difference and autoregressive models. Nevertheless, this is-
sue will be examined closely as risk factors are introduced into the analysis.

REFERENCES