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ERS/ATS workshop on longitudinal analysis of pulmonary function data, Barcelona, September 1995

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During the last two decades, longitudinal studies have been receiving increasing attention from many respiratory epidemiologists. In 1986, a workshop was held on methods for longitudinal data analysis, organized by the National Heart, Lung and Blood Institute. Statistical issues were discussed and new techniques were described. During the years following the workshop, the necessary software for performing these analyses became widely available. Currently, an increasing number of analyses have been published or are about to appear. For these reasons, epidemiologists and statisticians of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) thought it appropriate to organize a joint workshop in 1996 to discuss and update methods and results of longitudinal data analysis related to growth and decline of lung function (see list of participants at the end of the summary).

General issues

In an overview of the workshop issues, Weiss mentioned three reasons why longitudinal study designs are appealing: they offer the opportunity to study the temporal order of events, to observe individual patterns of change, and to measure exposure prospectively. The temporal order is essential to assess causality, making longitudinal designs superior to cross-sectional ones. Differences in age-related changes within and between individuals can be estimated with less bias caused by selective survival and cohort effects (although even longitudinal studies are not completely free of survival effects). Furthermore, longitudinal designs have greater power and precision than cross-sectional studies because between-individual variability does not contribute to the variability of individual change. In cross-sectional studies, exposures, such as cigarette smoking, have to be estimated retrospectively, and are thus more likely to be biased.

Weiss discussed several studies that illustrated these advantages. He also enumerated threats to the validity of longitudinal studies. Specific attention should be paid to: choosing the outcome variable; sample size and frequency of measurements; assessing quality control in order to minimize intrasubject variability (reduction of measurement error); and setting up procedures to minimize loss-to-follow-up. As Pope stated during the workshop, "No amount of statistical sophistication can compensate for sloppy study design or poor data collection".

Longitudinal studies present special problems of design, implementation and statistical analysis. Analytical methods depend on whether the outcome variable is continuous or categorical, whether the focus is on acute or long-term change in health status, and whether the analysis focuses on the pattern of the repeated measurements or the time to an event. The workshop and the related papers mainly discussed pulmonary function, specifically forced expiratory volume in one second (FEV_1), vital capacity (VC) and peak flow, (*i.e.* continuous outcomes). In addition, problems in analysing binary data and counts in time series analysis were discussed. The statistical methods and their applications related mainly to the modelling of repeated measurements at different time-points, with the exception of an innovating application of survival models for the analysis of the occurrence of bronchial hyperresponsiveness in challenge procedures.

Statistical issues

In his introductory paper, Ware specifically discussed methods for the analysis of repeated observations of FEV_1, aiming at the description of the effects of personal and environmental exposures on the trajectory of change over time. To achieve this, a model for age-related change in level of pulmonary function is needed. The life cycle of pulmonary function consists of three phases: growth to adulthood; plateau; and a period of age-related decline. Age-related changes during the preadolescent period can be described almost entirely by the dependence of the logarithm of FEV_1 on the logarithm of height. Data from the Six Cities Study provided evidence that, during adult life, FEV_1 adjusted for squared height (FEV_1/Ht^2) declined as a quadratic function of age. Furthermore, gender affected the level but not the rate of decline of FEV_1, thus interaction between age and gender was not required. Ware further discussed differences between cross-sectional and longitudinal estimates of decline, demonstrating that the individual rates of decline, estimated from longitudinal data, accelerated more rapidly than the cross-sectional data would suggest. As a consequence, the proportion of older subjects with a FEV_1 less than 80% of predicted (based on cross-sectional coefficients) was substantially greater than 5%.

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Having chosen an appropriate metameter for the dependent variable and a model to express the change in expected response with age or height and gender, one would like to model the association between personal or environmental exposures with pulmonary function level or rate of change. After having chosen a model of the correlation structure of the longitudinal data, one has to specify a model for the expected response. One simple and useful model is the two-stage growth curve analysis. In this approach, measures are described in an individual growth curve, assuming that the parameters of that growth curve vary randomly among individuals. In the first stage, regression coefficients can be estimated by fitting a straight line to each individual's observations and then, in the second phase, regressing these individual intercepts and slopes on the subjects characteristics, such as gender. More recently, a single general approach has been developed that fits a linear regression model to the entire data set, the marginal model. This model looks like the ordinary linear regression model, except that errors of different measures on the same individual must be assumed to be correlated. This approach has been extended to nonlinear models for repeated binary responses, known as the generalized estimating equation (GEE). In addition to modelling the expected response, one has to specify the form of the covariance structure as well as the form of the linear model. Candidate models include: the unrestricted covariance matrix; intraclass correlation matrix; and autoregressive models. Recently, Liang and Zeger introduced new methods for fitting regression models to repeated categorical responses.

Spline and smoothing approaches

Studying the effects of risk factors on pulmonary function requires appropriate reference equations for the dependence of lung function on metameters such as age and height. Normative models for lung function level can be estimated from cross-sectional studies. However, longitudinal studies are needed to allow assessment of the effects of exposures on change (growth or decline) over time. The linear modelling approaches usually applied in the adult part of the pulmonary function life cycle are only appropriate for use in children if the models are restricted to narrow age windows. Regression splines are nonparametric methods that can model the complicated dependence of lung function on age and height more flexibly. They can be used to determine which transformations to consider, or how to choose breakpoints in indicator variables in case the effects of a particular covariate, such as air pollution or smoking, are presumed not to be linear, and transformations or indicator variables corresponding to various covariate ranges are used.

In his contribution to the workshop, Wypij demonstrated the use of regression splines to model the effects of age and height on FEV_1 in 5,250 girls aged 6–18 yrs who participated in the Harvard Six Cities Study. He compared parametric models of the relationship between age and height and pulmonary function, with results from a more general model that allows age-dependent intercepts and slopes. The smoothing approach did not need the usual stratifications for different age ranges, nor the use of quadratic, cubic or other transformations of the covariates to assess nonlinearity. A particular advantage of regression splines is that standard regression packages can be used to fit models and to estimate standard errors, and the reference models can be used to assess effects of potential risk factors. From these analyses, it appeared that girls with asthma ever and current wheeze had a 3.6% deficit of their FEV_1 compared to symptom-free girls. The deficit was 1.0% for girls with current wheeze and no asthma, both differences being statistically significant. Thus, regression splines and other nonparametric techniques can be very useful as part of an exploratory data analysis, and as a method for having the data suggest the functional form of the model. Graphic and smoothing approaches to fitting the data are a helpful complement to standard regression methods.

Time series analysis

Pope and Schwartz explained that, in the case of repeated measures that are performed at frequent and equally spaced intervals over extended periods of time, time-series analysis is most useful. This is specifically so if short-term effects should be evaluated. The choice of a specific modelling technique depends on the objective of the study. If the movement of pulmonary function through time should be described, univariate time-series models can be used. If it is of more interest to make inference about relationships between risk factors and respiratory outcome, multivariate regression models should be fitted to time-series data. As any two variables, that show seasonal variation will be correlated, seasonal patterns and long-term trends should be accounted for in the analyses by dummy variables, sinusoidal terms or smoothing or filtering. Usually a regression model is fitted to the data and, for this type of continuous data, this will be a Gaussian multiple regression model. Most procedures can adequately accommodate nonconstant variance and autocorrelation that are most likely to be present in this type of longitudinal data. If binary data are studied, such as observations on symptom status, the data can be modelled in a logistic regression model, taking into account serial correlation of observations in the same participants (Liang and Zeger). A Poisson regression model can be used for count data, such as number of asthmatic attacks.

In addition to temporal colinearity, specific problems in time-series analysis relate to selection of the model and its functional form. Most models are special cases of generalized linear models. If the linearity imposed is hard to achieve, nonparametric models can be used that combine linear terms and nonparametric smooths (generalized additive models). Attention should be given to lag structures, because the effect of a current exposure may be partially due to a previous exposure. An "unrestricted distributed lag model" allows for an infinite number of lags. This type of model may introduce bias caused by multicolinearity between lagged exposure variables. Ignoring the lag structure may result in overestimation of the effect of the concurrent day's exposure, and an underestimation of the lagged and cumulative effect of several days exposure. "Restricted distributed lagged models" are an alternative approach, using weights that reflect the relative effects of current and lagged exposures.

Age, period and cohort effects

In his contribution, Lebowitz argued that cohort effects could be a partial explanation for the differences between longitudinal and cross-sectional estimates of change in lung function with age, as reported in various studies. Longitudinal data are necessary to be able to estimate the separate effects of cohort, age, and period (sum of age and cohort effects) on lung function. Results of analyses from a 25 year follow-up study were discussed. In one model, age, cohort and their interaction were included. In this model, the age coefficient was viewed as the "longitudinal effect" on lung function. The interaction (age·cohort) provided a test of the effect of cohort on age-related decline in lung function. A second model included age, period (4–5 year time intervals over the course of the serial surveys) and their interaction. In this model, the age coefficient was viewed as the cross-sectional effect of age on lung function. The interaction (age·period) provided a test of effects of survey period on the cross-sectional relationship between age and change in lung function. A relatively larger effect of cohort on estimates of decline was demonstrated. It is noteworthy that, although the analysis was entirely dependent on the longitudinal structure of the design and the longitudinal nature of the analysis, the focus of the inference was cross-sectional. However, in contrast to the usual cross-sectional analysis, the complex interplay of calendar and biological time on change in FEV_1 had been partially disentangled.

Generalized estimation equations and random effects models

The generalized estimation equations (GEE) and random effects model (REM) were discussed by Sherrill and Viegi. The basic models for REM and GEE include both overall effects, which are in general fixed effects, and within-subject effects that are often considered at random. GEE is generally used for categorical or non-normally distributed data. When used for normally distributed data, estimates from GEE tend to be biased in the case of considerable missing data (>20%). REM will be used when data are continuous, normally distributed or can be transformed to near normality, and have a lot of observations missing. For most applications, the coefficients associated with the fixed effects are of central interest, since they convey information about mean trends in relation to important covariables, such as smoking or air pollution. These effects are considered fixed, because these relationships are supposed to be similar for all individuals. In contrast, the within-individual relationship of FEV_1 with age may vary at random about the population mean curve. This is called a first order random effect, if individuals vary primarily in their intercepts but have similar slopes. If both intercepts and slopes vary randomly, then a second order random effect should be modelled. The need for random effects in the modelling and the order of the random effects, can be determined from parallel plots.

This graphical method, as shown in their paper, was most useful in studies with not too many observations. Sherrill and Viegi illustrated the use of the REM in data of the Tucson Study, and computing simulated data, going through the several stages of the modelling procedure. Their results suggested that the FEV_1 in lifetime nonsmokers was declining, on average, at a rate of 29 $mL \cdot yr^{-1}$, whilst in current smokers it was 44 $mL \cdot yr^{-1}$. Finally, they discussed assessing the model fit, using marginal and conditional residual plots.

Semiparametric and parametric survival models

A different method of analysing longitudinal data is achieved when focusing on modelling the time to a certain event, for which the methods of survival analysis are pertinent. Measuring bronchial responsiveness in a challenge test that uses increasing concentrations or doses of histamine or methacholine results in data whose characteristics are those of censored times in survival analysis. Muñoz and Sunyer presented results of a survival analysis applied to bronchial challenge data, using a semiparametric model of proportional hazards and a parametric model, where the hazard of responding increased monotonically with dosage. Concentration was used as time, and response (a decrease of 20% in baseline FEV_1) as the event. Nonresponding subjects with incomplete protocols and subjects free of response at the maximal dose were considered censored. The proposed parametric models provided direct estimates of whether a given covariate (*e.g.* smoking) increased or decreased the concentration at which a given percentage of individuals responded. The semiparametric and parametric models were implemented on 512 nonsmokers and 1,014 smokers participating in the Spanish centres of the European Community Respiratory Health Survey (ECRHS).

Life table procedures produced a satisfactory analysis of bronchial responsiveness in population studies. In the analysis of bronchial responsiveness data, the roles of origin, time and event in standard survival analysis data were played by saline inhalation, concentrations of methacholine, and 20% decline in FEV_1, respectively. A comparison was made between the commonly used Cox regression and a Weibull model where hazard of response increases monotonically with the concentrations given. If the hazards fulfilled the assumption of proportionality and the distribution of the concentrations followed approximately a Weibull distribution, the two approaches gave identical results. Nonproportionality of hazards could be incorporated by the Cox model with the inclusion of an interaction between the variable of interest and concentration (*i.e.* time), and in the Weibull model with different scales for groups defined by the variable of interest. After incorporating the nonproportionality of hazards of response for smokers and nonsmokers, both approaches were equally informative for estimation and inferences using relative hazards as the measure of the effect of smoking on bronchial responsiveness. An alternative measure for comparing groups was the relative percentiles which, in many instances, were a preferred descriptor of differences between groups. With respect to estimation and inferences using relative percentiles, the Weibull approach provided a direct and simple procedure.

Childhood respiratory infection and growth and decline in lung function

In many studies, lower respiratory infection (LRI) in childhood has been demonstrated to be associated with lower level of adult pulmonary function. In general, hypotheses tended to suppose that LRI caused the lower level of pulmonary function. However, only studies with a longitudinal design, starting at birth and following up the subjects in their first years of life, can provide insight into the temporal order of events.

The importance of longitudinal studies was demonstrated by the contribution of Britton and Martinez. They reviewed the existing evidence pointing to the great difficulties that may occur in measuring outcome and risk factors (lung function in newborn infants, assessing viral infections), and problems related to information bias in retrospective studies. They reported on the results of the Tucson follow-up study in newborn children, revealing that lower pulmonary function preceded the increased risk of LRI. For maximal ventilation at functional residual capacity ($V'_{max,FRC}$), deficits reached 20–30%. Other prospective studies by Tager and by Young reported similar results. These results may create problems in interpreting the relationship between childhood LRI and adult chronic obstructive pulmonary disease (COPD). This relationship may arise, at least in part from "confounding" factors causing low lung function in infants. Candidate confounding factors are: parental smoking, specifically maternal smoking during pregnancy; socioeconomic factors, birth weight; and gestational age. It is also possible that there are different forms of LRI with different aetiological and pathogenetic factors, and with different relationships to adult COPD. To answer these and other questions, follow-up is needed, preferably from birth to senescence.

Airway responsiveness

Another example of the need for longitudinal studies to sort out the temporal order of events was given by Rijcken and Weiss in their presentation on airway responsiveness and decline in pulmonary function. Essentially, there are three ways to explain a low level of FEV_1 in adulthood: a lower maximal attained level; a steeper decline; and an earlier onset of decline, or any combination of these three mechanisms.

In the Dutch longitudinal study on risk factors of COPD, the Vlagtwedde-Vlaardingen Study, repeated measurements of FEV_1 and a series of risk factors, including airway responsiveness, have been collected between 1965 and 1990. These data have been analysed using a variety of statistical techniques, including smooth and spline techniques, an autoregressive model, a general linear model with intraclass correlation, and a random effects model. In all of these analyses, airway hyperresponsiveness was associated with accelerated decline of FEV_1, independent of smoking and other risk factors.

In the final analyses, change of FEV_1 with time was analysed, measuring airway responsiveness and all other risk factors at the beginning of the follow-up interval. Because level of responsiveness and level of pulmonary function were related and level of lung function was related to decline, the analyses were adjusted for initial level of FEV_1. The association of airway responsiveness with annual rate of decline was estimated by ordinary least square regression. The variance of the estimated parameters was calculated by a generalized estimating equation and robust estimates of the standard errors (Liang Zeger method). There was an excess mean annual loss of FEV_1 for hyperresponsive males of 12 $mL \cdot yr^{-1}$ and for females of 11.5 $mL \cdot yr^{-1}$, independent of smoking, symptoms, area of residence, age, period, and initial lung function level.

In a separate analysis of subjects aged 15–35 yrs at inception of the study, airway hyperresponsiveness was associated with a 225 mL deficit in maximal level attained for males and 213 mL for females. Other factors predicting lower maximal level of FEV_1 attained were the presence of symptoms and an increased number of eosinophils. In these data, cigarette smoking predicted lower maximal level attained in males but not in females. From additional analyses, it appeared that maximal level attained, as such, was a strong predictor of lower level of FEV_1 in later adult life (age 35–55 yrs). It was concluded that airway responsiveness was associated with accelerated decline in FEV_1, and was a predictor of lower maximal level of FEV_1 attained. This implies that the preclinical course of airway obstruction may have already started early in life. Thus, prevention, and possibly intervention, should start early.

Air pollution

Longitudinal changes in lung function related to air pollution can be studied over many different time periods, ranging from minutes, hours, days, weeks, months or seasons to years. Dockery and Brunekreef reviewed a selection of the many published studies, illustrating methodological and analytical issues. In air pollution studies, careful measurement of the level and character of the exposure is essential. The very short-term effects were often studied in laboratory conditions, comparing effects of exposure to filtered air *versus* air pollution, or under different levels of ambient outdoor exposures during field studies. Complicating factors were: the interaction with (or confounding by) temperature; and diurnal variations in level of lung function values. Analytical problems were limited. In studies of changes over days, the same population was measured repeatedly, participants serving as their own controls. For panel studies over a longer period, diurnal effects may also complicate the interpretation of results. Training effects and, specifically in children, growth effects could also interfere.

Studies in daily changes in lung function have generally been analysed using linear regression techniques. A clinical study over months showed a seasonal effect in the acute response to ozone. The acute response to ozone present in the spring could not be demonstrated during the autumn and the winter, but returned in the following spring. A number of studies covered a follow-up period of several years. In that type of study, shorter term influences might have caused short-term changes, often treated as sources of random error in the longitudinal analysis.

In general, the effects of growth and ageing were greater than the posited cumulative effects of air pollution. Careful controlling for smoking was necessary. Air pollution measured over a longer period could vary with time, posing specific problems to the analysis. In addition, other time-varying variables had to be modelled. This also implied that acute (short-term) studies had more statistical power because all other variables tended to be equal and only air pollution levels changed. In studies of effects of air pollution, confounding by age and other time-dependent covariables might become larger than the expected effects of air pollution. The ultimate consequence was that, for studying the effects of air pollution, longitudinal studies over years might not be more efficient or powerful than cross-sectional studies *per se*.

Active and passive smoking

Samet and Lange reviewed a substantial body of longitudinal data showing that a great deal has been learnt about the impact of passive and active smoking on lung function. The data have been analysed with methods of increasing sophistication, moving from two-point or linear regression estimates of change to more recent models that utilize the more fully longitudinal information. The longitudinal data and complementary cross-sectional evidence have already been sufficient to support conclusions as to the effects of passive and active smoking on lung function. Substantive questions remained, however, and these questions would require longitudinal data. Up to the present time, age-specific segments in the life cycle of pulmonary function have been addressed and the effects of smoking characterized within the age windows. However, the transition between childhood and adulthood has received little investigation, and the consequences of passive smoking during childhood as well as early active smoking for subsequent decline of lung function have not been assessed. There was still only limited information on the effect of *in utero* exposure and on the extent to which there were independent effects of *in utero* and early childhood exposures to maternal smoking. In their simplest form, the three exposures were dichotomous variables (yes/no) for: 1) passive smoking *in utero*; 2) passive smoking in early childhood; and 3) active and passive smoking in subsequent years. Studies are needed to provide sufficient sample size in each of the eight categories defined by the three exposures, so that proper comparison of the trajectories of the lung function in the groups can be accomplished.

Obtaining answers to these questions is not hindered by availability of analytical techniques. A biologically-based model has been postulated and appropriate model-fitting techniques are available. Rather, our ability to answer these questions will be limited by the availability of data. It is impossible to achieve lifetime information that begins with pregnancy and then extends across the full lifespan. On the other hand, this information could be obtained if data from different cohorts were pooled. New methods are needed to juxtapose one cohort with another, so that they provide complementary information to describe the mean trajectories over the full range of the life span. Recently, methods to juxtapose incident and prevalent cohorts in infectious disease epidemiology have been developed and implemented to describe the incubation period of acquired immunodeficiency syndrome (AIDS). In the context the epidemiology of respiratory disease, the juxtaposition would not be based on failure times but on markers of disease progression. The data available correspond to markers at a limited range of ages for different individuals. Assuming that comparable individuals (according to known predictor of lung function) replicate the trajectories of lung function, the pooling of different cohorts is feasible. It seems unlikely that data from additional large cohorts will be available on a short-term basis. Creative approaches for pooling existing data may allow investigation of questions that may be left unanswered by individual studies.

Risk factors for accelerated decline in COPD patients

Risk factors for accelerated lung function decline in patients with established obstructive lung disease were reviewed by Kerstjens and Postma. The interpretation of studies of decline of FEV_1 in patients with established COPD was complicated by many methodological problems, such as retrospective analyses, small patient groups, differences in patient selection, and differences in the mathematical models used. The major determinant of rate of loss of pulmonary function in patients with COPD was their current smoking status and their smoking history. A more abnormal bronchoconstrictor response was also predictive of a steeper decline of lung function. Results of studies on the prognostic value of the bronchodilator response were conflicting. Other prognostic factors have not been consistently identified in patients with established disease. Specifically, it could not be demonstrated that low initial level of FEV_1 predicted accelerated rate of loss of lung function in COPD patients.

For purposes of analysis, it is important to realize that the course of the change of lung function with time in patients with COPD did not need to be linear, especially in the case of interventions. Nonlinear patterns included those with an initial increase followed by accelerated decrease, and those with an initial decrease followed by increase of lung function. The overall decline could be influenced favourably by smoking cessation, and probably by administration of oxygen in hypoxaemic patients. Maintenance therapy with bronchodilators as a single therapeutic did not appear to slow the decline of FEV_1. There was some evidence that use of long-term oral steroids was associated with a more favourable course of FEV_1. The effectiveness of inhaled corticosteroid therapy in patients with COPD awaits the results of two large European intervention studies, the European Respiratory Society Study on COPD (EUROSCOP) and Inhaled Steroids in Obstructive Lung Disease (ISOLDE).

Interpretation of longitudinal studies

Schouten and Tager reviewed the possibilities and problems in interpreting results from longitudinal studies.

Central issues were the temporal order of events, individual patterns of change and assessment both of level and change. The design of and the analytic approach to a study depend on where the emphasis was. They discussed, specifically, the interface of longitudinal and cross-sectional data. Although studies had a longitudinal design, often data were analysed as if they were cross-sectional. The inference at the statistical level was to the mean level for a population (or subgroup of a population) at a particular age. Because the degree of tracking was high, longitudinal inference was appropriate. Various studies were discussed illustrating the various problems, including period and cohort effects. Specific attention was given to the need for adjustment for initial level of FEV_1 in longitudinal data analysis. Regression to the mean effects and horse-racing effects were discussed. In general, when the initial level reflects the past effect of a covariate, adjustment for initial level may be appropriate, however, overadjustment could occur resulting in underestimation of the effect of the covariate.

In evaluating the change of lung function with age in data collected over an extended period of time, nonlinearity of the relationship between change and age may present problems. More flexible methods have become available to cope with this problem, including nonparametric and semiparametric smoothing techniques. These techniques are also applicable in studies of lung function growth in childhood and adolescence. Longitudinal studies make possible a range of inference concerning pulmonary function, particularly at the level of the individual, that is not possible in cross-sectional studies. Such inference has important implications for aetiological epidemiology and for clinical practice. Longitudinal studies have provided a clearer insight into the natural history of change in lung function and the factors that influence it during various epochs of life. Importantly, longitudinal designs have provided an opportunity to separate out the process of change from the levels of lung function of individuals at the start of any given study and have helped to establish temporal, aetiological relationships (*e.g.* airways hyperresponsiveness and decline in lung function).

However, as has been demonstrated, longitudinal studies are often analysed and presented in such a way as to focus on the cross-sectional (population mean) aspects of the data, and such presentations have provided important and useful insights at the level of the individual. If population mean effects are the goal of inference, when are longitudinal studies to be preferred over cross-sectional studies (independent of issues of study costs and logistics)? Several circumstances can be suggested: 1) when outcomes and exposure are measured substantially more precisely within individuals compared to between individuals; 2) when period and or cohort effects are likely to be important; and 3) when temporal sequence has not been well-established. In those circumstances where measurements in individuals may be highly imprecise, relative to population means (*e.g.* studies of the effects of long-term exposure to high levels of ambient air pollutants on lung function) cross-sectional studies, in fact, may be a preferred strategy.

Recommendations

All participants agreed that this workshop was an exciting experience, making an important contribution to the exchange of ideas and stimulating discussion concerning methods and applications. This meeting should be followed by further initiatives for co-operation and exchange of expertise and knowledge between European and American researchers. General recommendations include:

1. To stimulate the application of novel statistical methods and enhance the introduction of these methods to a wide audience both of epidemiologists and clinicians.
2. To reanalyse existing data sets using new and more appropriate statistical techniques than those that were available at the time the studies were published.
3. To pool data from various studies, specifically on active and passive smoking.
4. To stimulate co-operation between different research centres in order to use data from various age-groups to piece together the complete pulmonary function life cycle from birth to senescence.
5. To stimulate studies and data analysis of the plateau phase.
6. To stimulate co-operation between epidemiologists and clinical researchers and to implement novel statistical methods specifically in studies of patients.
7. To promote standardization of clinical assessment of symptoms, treatment and lung function in order to enable pooled analysis of data from different patient populations.

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