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Outcomes in Cohort Studies

Ira B. Tager

INTRODUCTION

The initial intellectual appeal of the cohort design for epidemiologic studies stems from the obvious fact that the method of subject selection leaves little doubt about the temporal relation between the exposure and the disease whose relation is under study. The inferential power of this fact clearly was realized by Doll and Hill in their landmark 1954 publication (1) in which they explicitly acknowledged the need to observe the "future" outcome (lung cancer) of disease in those whose exposure (cigarette smoking) is already known antecedent to the disease. Minimization of recall bias (in relation to exposure) and selection bias based on exposure, and to some extent on disease outcome, are benefits of cohort studies, although modern case-control studies that are based on techniques of risk-set sampling from cohorts or case-cohort designs have blurred some of the distinctions between the benefits of cohort versus case-control studies (2) with regard to issues of temporal sequence and selection bias. Cohort studies nonetheless retain the unique capacity, vis-a-vis any type of sampling design for case-control studies, to evaluate multiple outcomes as a consequence of given exposure, to study temporal processes of disease onset and progression ("natural history" study), and/or the biologic/physiologic processes that underlie the subsequent occurrence of a disease.

To organize this discussion of the types of outcomes that can be derived from cohort studies (table 1), I have found it useful to divide cohort studies into two broad categories, "life table-type" and "longitudinal." The former are characterized by their treatment of time and exposure in a manner that is closely tied to traditional life table methods of analysis. In general, exposure and person-time are summarized, and incidence (density), cumulative incidence of a discrete disease outcome, and their respective ratios are the prinicpal outcomes of the life table-type cohort study. Inferences from theses types of cohort studies are restricted to population average effects. Longitudinal cohort studies, on the other hand, take explicit advantage of the repeated measures characteristics possible in cohort designs and make possible not only inferences on population average effects but on individual heterogeneity, changes in processes over time, and transitions between states of health and disease. Although this distinction is somewhat artificial, since all cohort studies make at least two repeated measures, it will serve as a useful framework within which to discuss the range of outcomes to be derived from cohort designs.

I have chosen examples to illustrate the various types of outcomes in cohort studies. While I have drawn heavily from my own interest in chronic respiratory disease and cigarette smoking, I also have selected examples from epidemiologic studies of cardiovascular disease, human immunodeficiency virus (HIV) infection, and aging. The purpose of the examples is not exhaustive coverage of all possible design outcomes or critique of the studies per se, but, rather, it is to identify the salient features through which various types of outcomes can be derived from cohort studies. I only allude to the specific methods of analysis, since these are covered in subsequent papers.

THE "LIFE TABLE-TYPE" COHORT STUDY

The 1970 textbook, *Epidemiology: Principles and Methods* by MacMahon and Pugh (3), defines the distinguishing features of cohort studies as follows:

> 1. The group or groups of persons to be studied. . .are defined in terms of characteristics manifest prior to the appearance of the disease under investigation.
> 2. The study groups so defined are observed over a period of time to determine the frequency of disease among them (3, p. 207).

In one form or another, virtually all current introductory (4), intermediate (5), and more advanced epidemiology texts (6–8) discuss the cohort study in the context of this definition. Some authors (6, 7) have noted the longitudinal (repeated measures) character-

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Abbreviations: COPD, chronic obstructive pulmonary disease; EPESE, Established Populations for Epidemiologic Studies of the Elderly; FEV_1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus; PGV_{ind}, individual peak growth velocities.

From the Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, CA.

TABLE 1. Types of outcomes for cohort

Discrete events
Single events
Mortality
First occurrence of a disease or health-related outcome
Incidence (density)
Cumulative incidence (risk)
Ratios (incidence density and cumulative incidence)
Multiple occurrences:
Of disease outcome
Of transitions between states of health/disease
Of transitions between functional states
Level of a marker for disease or state of health
Change in a functional/physiologic/biochemical/anatomic marker for disease or health
Rate of change
Patterns of growth and/or decline
"Tracking" of markers of disease/health
Change in level with time (age)

istics and potential of cohort studies, and have presented the basic structure of the "natural history" study (6). However, even in these latter cases, the focus in on the estimation of incidence for a group over specific intervals of time (6). Thus, in the above characterization of the cohort study, the principal measures of outcome occurrence are incidence (incidence density, cumulative incidence) of *states* of health or disease and/or overall and cause-specific mortality. Consequently, there is a direct parallelism between the inferences derived from this type of cohort study and the analysis of a life table (9). For want of a better term, I will refer to such cohort studies as "life table-type cohort studies" as indicated above..

The summarization of time and exposure is the hallmark of the life table-type cohort studies (table 2): 1) summary of time to produce cumulative incidence or average incidence density over the period of observation; 2) summary of exposure to produce baseline and/or accumulated exposure over the period of observation. The summarization of exposure over time leads to the partial unlinking of the exposure effect from the details of time over which the exposure exerts its effect(s). This is equivalent to the implicit assumption that the exposure operates at a constant level (mean over time) and has a constant effect per unit time over the entire exposure period of the cohort or within partitions of the exposure period (i.e., specific age ranges). This situation occurs independent of any strategy to model the shape of the exposure-outcome relation (10) so long as the estimation of shape of the exposure-response relation is based on some overall summary (over the observation time of the cohort) for each individual's exposure. As a consequence of the summarization process, life table-type cohort studies, in general, do not, or cannot, provide inferences on process (see below) and can provide only limited indirect inference on the time-dependence of the exposure-outcome associations.

Given that this type of cohort study is most familiar and has a long history of use in epidemiology, only two examples of life table-cohort studies will be invoked to illustrate the above points and to sharpen the focus on the type of inference that can be derived from such studies. Each example study was undertaken to determine, at the population level, the effect of an exposure, although in one case the inference moves to the level of individuals. Both studies involve health professionals and are separated by two decades in time (table 3).

The British Doctors Study

The British Doctors Study, which was initiated in 1951 to evaluate the relation between cigarette smoking and lung cancer (1), reported its 20-year follow-up in 1976 (11). At the time of this report, the investigators had obtained a baseline (1951) and two additional (1957, 1966) questionnaire evaluations of the smoking histories of the subjects. Mortality data were obtained. Individual person-years of follow-up for each member of the cohort was assigned to smoking-specific 5-year age groups from ages 20 to 84 years, and age 85 years and older. The assignment by age-specific categories is an implicit recognition that the passage of calendar time may have different effects on risk at different ages. The person-year data were aggregated to produce estimates of overall annual incidence of various

TABLE 2. Characteristics of "life table-type" and "longitudinal" cohort studies

Characteristic	Comment
Subject selections	
Life table-type	
Exposure status at the inception of cohort	Need to assure that each exposure group is representative of those with similar exposure status in the target population for the cohort
Longitudinal	
Exposure status at inception of cohort	Same as for life table-type cohort study
Can be unrelated to status on single, explicit exposure ("natural history" study)	Subjects should be representative of target population in general Target population could be subjects with defined health condition(s)
Time	
Life table-type	
Summarize	Cumulation of person-time to estimate cumulative incidence and/or average incidence density over the entire period of follow-up and/or over specific age or time epochs encompassed by the cohort Typical formulation of time-dependence retains features of group person-time summarized over subintervals of follow-up
Longitudinal	
Summarize	Same as for life table-type cohort study
Effects evaluated explicitly	Can separate cohort and age effects Can evaluate/model time-related associations between observations over time Can evaluate "tracking" (correlation of outcome over various time intervals)
Exposure	
Life table-type	
"Baseline"	Exposure classification based on initial entry into the cohort ("baseline") often
Summarize/categorize	used to characterize the exposure experience over the entire follow-up of the cohort Updated exposure summarized into cumulative measures (continuous or ordinal), state measures (e.g., none, current, past), or combinations Averages exposure over the period or subperiods of observation
Longitudinal	
"Baseline"	Same as for life table-type cohort study
Summarize/categorize	Evaluate effects of exposure in addition to effects attributed to exposures
Time-dependence of effects more explicitly formulated	accumulated up to the time of cohort inception ("baseline") Distinguish effects on individuals from population average (cross-sectional) effects Evaluate exposure-effect associations at any given time point in history of subjects Evaluate current exposure conditional on past exposure profiles
Outcome	
Life table-type	
The first recognized occurrence of a disease or other health-related *state*	Not well suited to outcomes that are "continuous" Such outcomes often reformulated into categorical (*state*) outcomes
Overall and/or cause-specific mortality	Measures: incidence density, cumulative incidence, and their respective ratios for "exposed" and "nonexposed"
Longitudinal	
The first recognized occurrence of a disease or other health-related *state*	Same as for life table-type cohort study Description of "natural history" of a health condition
Overall and/or cause-specific mortality	Description of physiologic processes that are precursors to discrete health conditions
Rate of change (growth, decline)	Eliminates restriction to first occurrence of health conditions
Transitions between states of health	
Tracking	
Inference	
Life table-type	
Population or group average effects	Inference properly limited to groups and not individuals Cumulative incidence refers to *average* individual risk and not relevant to any specific individual
Longitudinal	
Population or group average effects	Same as for life table-type cohort study
Inference at the level of individuals	*Natural history* refers to description of changes over time: in physiologic/biologic markers
Natural history of states of health and disease and important physiologic processes	of disease pathogenesis; in expression of particular manifestation(s) of disease or general markers of health; in the relation between exposure and outcome; in growth and decline of anatomic/functional/physiologic characteristics with general health implications

cancers and other "diseases associated with smoking" (11) and age-specific annual death rates. To accommodate the complexity of smoking behaviors, the authors created a variety of summary measures (table 3) to capture the duration, intensity pattern (inhalation) of smoking, and the types of tobacco use.

In terms of the outcomes of interest, the issues are straightforward. The goal was to estimate the relation between cigarette smoking on the annual incidence of a variety of cancers and other diseases that were thought to be associated with smoking. The choice of incidence (density) clearly indicates the etiologic fo-

TABLE 3. Examples of outcomes and exposure in two cohort studies analyzed as "life table-type cohort studies"

British Doctors Study, 1976 (1)		Health Professions Follow-up Study, 1993 (13, 14)	
Measure	Implementation	Measure	Implementation
Outcome		Outcome	
Age-standardized annual death rate * 10^{-5}	Person-years allocated to relevant age-specific intervals	Cumulative 4-year incidence	Person-years not assigned on age-specific basis
Age-specific annual death rates 1951–1971 (5-year age intervals)	Overall and age-specific annual death rate from: Lung and other cancers Ischemic heart disease "Other" conditions	Relative risk (cumulative incidence) inferred from incidence rate ratios	Incidence rate ratio interpreted as relative risk across exposure categories Summary measure over 5-year age groups—appears to be age at last examination
Exposure		Exposure	
Use of cigarette and other tobacco products Amount, duration, inhalation Ascertained on three occasions, 1951, 1957, 1966	Aggregate smoking history summarized into several different categorical classifications 1. *Table III*: Non-smokers, current/ex-smokers, ex-smokers current smokers, any tobacco; current smokers, any smokers (*gm/ day*: 1–14, 15–24, ≥25) 2. *Table III*: Non-smokers, cigarettes only, pipe and/or cigar, mixed use, current cigarettes (gm/day: 1–14, 15–24, ≥25 3. *Table VII*: Smokers—inhale, do not inhale	Vitamin E, vitamin C, β-carotene intake from foods and supplements Accessed on three occasions, 1986, 1988, 1990	Summed over the 3 years and categorized as quintiles of intake/day 1. *Table 2*: From food 2. *Table 2*: From supplements 3. *Table 3*: Years of supplement use

cus, at the population level, of the inference (6). The method for the aggregation of person-time provides several measures of *average incidence* of the cancers and other outcomes of interest: 1) average incidence over the entire 20-year period of follow-up and 2) average incidence over 5-year epochs within the age-range of the cohort. The focus of inference is the comparison of annual incidence of disease between *groups* of individuals who are distinguished by their smoking histories. The temporal behavior of most of the cancer outcomes (11, table III) also is relatively straightforward—i.e., multiple new occurrences of a given cancer type usually do not occur in a given individual (occurrences of different cancers in a given person clearly are more likely to occur), and the focus of the etiologic inference is such that this issue is not necessarily central.

The treatment of exposure in the British Doctors Study is less straightforward. Since smoking habits are quite variable in terms of current status (smokers quit and restart), amount smoked (current daily consumption may not reflect typical past consumption), details of use (depth of inhalation), and types of tobacco products, the summarization of exposure had to take several forms (table 3). The classification includes current status with regard to overall history (e.g., nonsmoker, current/ex-smoker; nonsmoker, any tobacco; categories of amount smoked by current smokers). The exposure-response modeling of the amount smoked versus incidence of lung cancer (12) has the same population focus that would be obtained in a cross-sectional study—i.e., the individuals' average current daily exposures are evaluated in relation to lung cancer incidence (12, figure 1), and lung cancer incidence is modeled as several functions of lifetime duration of smoking (12, figure 2). For both summaries, the exposure has been unlinked from the specific elements of real time over which it was accumulated. Despite this unlinking, the title of the paper that relates to the exposure-response modeling is "Cigarette smoking and bronchial carcinoma: dose and **time** [my boldface] relationships among regular smokers and lifelong non-smokers" (12). "Time" in this study clearly is aggregated population-time and not individual-time. In the end, what distinguishes the inferences that are derived from this report of the experience of British Doctors Study cohort from that of a cross-sectional study of the same population at the same time (as the 20-year follow-up was conducted) has less to do with the fact that several measures of exposure were available and more to do with the certainty that the estimate of the exposure summaries was not influenced by knowledge of the outcome, and that there was no selection bias based on the outcome—not an inconsequential point of difference. Nonetheless, in a cross-sectional study, all of the actual summaries of exposure could have been obtained, and the person-time experience of the cohort would have been captured implicitly in the prevalence odds ratio (as an estimate of the incidence density ratio, given that smoking status does not affect lung cancer survival (6)).

The Health Professionals Follow-up Study

This prospective cohort study enrolled a wide range of health care professionals between the ages of 40 and 75 years and was begun in 1986 to study the relation between diet and heart disease and cancer (13, 14). Subjects underwent a baseline examination that included dietary assessment and assessment of underlying coronary heart disease. Reassessment was undertaken in 1988 and 1990 to ". . .update. . . exposure and to ascertain events related to newly diagnosed coronary disease" (14, p. 1450). The 1993 report of Rimm et al. (14) focused on the relation between intake of vitamins E and C and newly diagnosed coronary events. To assure that disease status did not influence the exposure, only men without clinically recognizable cardiovascular disease were included in this report. This inclusion criterion reflects a clear difference between the outcome in this study and the cancer outcomes in the British Doctors Study. Multiple occurrences of coronary artery disease *events* clearly do occur. Such events could, and often do, influence the health behavior (diet in the case of this study) of individuals, and the effect of the exposure could be dependent on the status of individuals in relation to his/her past history of relevant events. This approach—limitation to first events—is a typical, although not necessarily satisfactory, solution in the life table-type cohort study to the problem of multiple event occurrence.

Person-time is treated differently in the Health Professionals Study than in the British Doctors Study. Unlike the British Doctors Study, person-times were assigned without age specificity, i.e., each year of person-time was assumed to carry the same risk for coronary heart disease without regard to the known increased risk with age. Incidence rate ratios (referred to as "relative risk" (14)) were summarized over 5-year age groups apparently without regard to age-specificity of person-time; each finite unit of person-time carries the same instantaneous risk (incidence). In aggregate, the summary measures are treated more as cumulative incidence than as incidence density. Given that cumulative incidence is interpreted as the average risk (probability) that an *individual* develops a first coronary heart disease event over a *specified period of time* (5), the focus of inference of this study clearly differs from that of the British Doctors Study despite the direct measurement of the same measure of outcome—incidence density. As presented, the age and duration-of-time specification of the average individual risk is lost. Such losses of the time references that are imbedded within a specific cohort are not unusual for life table-type cohort study designs.

The treatment of exposure (table 3) is similar to that described for the British Doctors Study and involved the development of several categorical summaries of the past years' intake of dietary sources of vitamin E and total duration of use of supplements. Time-dependent elements of exposure cannot be evaluated in this formulation and, implicitly, exposure is assumed to operate uniformly over time. However, given the inferential focus on cumulative incidence (relative risk) and, thus, (average) individual risk, one is led to consider some questions whose investigation is obscured by broad summaries of exposure over time. For example, it might have been of interest to determine whether it was the reported cumulative exposure to vitamin E at the time of the initial examination (which could reflect anywhere from 40 to 75 years of exposure) and/or the exposure during the follow-up years that conferred the apparent coronary heart disease-sparing effects that are presented. This type of analysis would permit indirect inference on the critical times during which antioxidants might exert their protective effects and would have provided some insight into etiology—effects attributable to intake during the follow-up would suggest that antioxidants not only might be protective but also capable of reversal of any clinically unrecognizable coronary artery disease that was present at the time the cohort was recruited. Survival analysis techniques that allow for time-dependent effects of exposures and covariates (confounders and effect modifiers) permit this type of inference to some degree (15). A more explicit treatment of time and disease state also would permit the inclusion of persons with clinically recognized coronary artery disease at the baseline evaluation and allow for a more explicit inference on the effect of cumulative and current (time-dependent) antioxidant intake on preexisting coronary artery disease as well as on first-time events. Here the focus is on transitions in exposure and/or disease state and falls outside the typical life table oriented focus of this type of cohort study in which only a single transition stage (e.g., nondiseased to diseased) is considered.

Comment

The two cohort studies discussed in this section are typical examples of the way in which life table-type cohort studies have been used. The British Doctors Study illustrates the effectiveness and relative strength of this type of cohort study for etiologic inference at the population level. While incidence density (rate) ratios and cumulative incidence (risk) and cumulative incidence ratios were not presented, such outcome measures easily could be derived from the data presented.

Although a completely typical life table-type cohort study in terms of outcomes, analysis, and inference, the Health Professionals Study provides a useful example of the limitations of the usual life table-type cohort study when the target inference is risk. The risk that is estimated in this study is average individual risk within the group that was studied, and, as such, has no direct interpretation at the level of any given individual, however important or desirable such an estimate might be. Time and exposure are summarized at the population level, and the time-dependence, such as it might be accounted for in this context, retains the population-level focus. Time-dependence of exposure is estimated in the life table-type cohort, in effect, by the serial evaluation of the exposure (and covariate) characteristics of the subjects who were at risk at the start of a time interval and did or did not experience the health event (e.g., first-time coronary artery disease event). The evaluation is carried out over all of the time intervals of observation (two in the Health Professionals Study) as if each were its own small cohort substudy (15) and without an explicit formulation of the dependence on the previous status of each individual subject with regard to exposure or other characteristics of interest.

THE "LONGITUDINAL" COHORT STUDY

Although all cohort studies, by definition, make more than a single measurement on the study subjects, I apply the term "longitudinal" to those cohort studies that make repeated (more than two) measures (16) of exposure and outcome over time and whose inferential and analytic focus includes interest in any of the following: 1) estimation of effects at the individual level (e.g., heterogeneity between individuals, comparison of exposure-outcome response relations based on cross-sectional "baseline" data versus that based on longitudinal data (17, 18)); 2) estimation of the effects of changes in risk markers over time on disease (health state) outcome; 3) estimation of rate of change or change in level with time for some outcome that relates to disease natural history (includes growth, decline, and tracking of anatomic/functional/physiologic processes that are related to a particular state of health or disease; e.g., forced expiratory volume in 1 second (FEV_1) and chronic obstructive lung disease, serum low density lipoprotein cholesterol and coronary heart disease); 4) natural history of states of health that either have multiple occurrences or can oscillate between different states (e.g., functional disability in the elderly (18)); and/or 5) separation of cohort (or period) effects from the effects of age or chronologic calendar time (table 2). Longitudinal cohort studies also can provide all of the inferences of the life table-type cohort study that were discussed in previous sections. These are noted in table 2 but are not commented upon in the examples.

Estimation of effects at the individual level, individual heterogeneity, cross-sectional versus longitudinal inference

Identification and quantification of individual heterogeneity is of interest for several reasons. From the point of view of etiologic inference, the identification of "sensitive" phenotypes may provide important clues for the understanding of the determinants of disease occurrence. From the population perspective, the decision about the interpretation (and to some extent the validity) of population average effects depends in part on the degree of heterogeneity between individuals with respect to a particular exposure-outcome relation. Finally, it may be of importance to evaluate the extent to which inferences that are obtained from cross-sectional studies are comparable with those that would be obtained in a more demanding and expensive longitudinal study (which, in fact, is a restatement of the idea in the previous sentence). A series of studies by Dutch investigators that relate to chronic respiratory disease illustrate all of these points (19–21).

Figure 1 presents data on the peak growth velocity for FEV_1 in a group of 144 Dutch children with an average age 12.7 ($\pm$0.5) years at enrollment and who were observed at 6-month intervals for 7 years and for whom at least nine measurements were available. FEV_1 is of considerable importance in respiratory epidemiology since its patterns of growth and decline are thought to be related to the risk of chronic obstructive lung disease in adult life (22). It is clear from the figure that there is substantial heterogeneity in the individual peak growth velocities (PGV_{ind}). Moreover, the population average growth velocity curve that was derived from all of the individual data points for all subjects substantially underestimates the overall level of peak growth compared with an average of the individual peak growth velocities (median peak of PGV_{ind} = 0.65 liters/year versus 0.49 liters/year from the population estimate). These same investigators also evaluated the effects of respiratory illness experienced in childhood with growth of FEV_1 over ages 12–18 years. Growth curves were fitted for each child. At each 6-month observation, the growth of FEV_1 in liters/year was estimated. From the analyses in figure 2, the investigators were able to conclude that respiratory illnesses early in life exert a carry-over effect on levels of FEV_1 but do not effect patterns of growth during the adolescent years. Thus, cross-sectional differences in PGV_{ind} between children with and without such a history would not be expected to be due to the

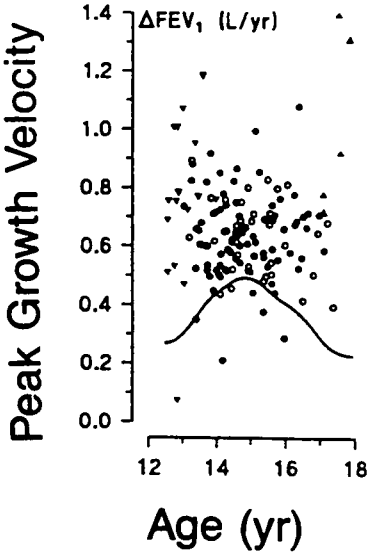

FIGURE 1. Plot of individual peak growth velocities (PGV_{ind}) of forced expiratory volume in 1 second (FEV_1) versus age. Solid line is population average growth velocity based on data for all time points of observation for all subjects. Open circle (○)/open triangle (△) = healthy subjects; closed circle (●)/closed triangle (▲) = subjects with respiratory illness before puberty; ▲ are PGV_{ind} for those whose age peak growth was estimated to have occurred after the last FEV_1 measurement, ▼ are PGV_{ind} for subjects whose age at peak growth was estimated to have occurred before the first FEV_1 measurements. From figure 1 of Borsboom et al. (21); reproduced with the permission of the American Lung Association.

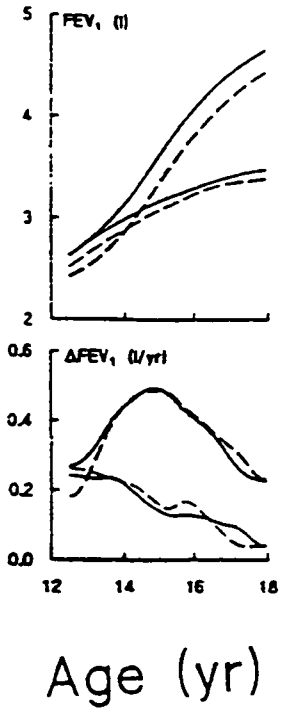

FIGURE 2. Average growth and growth velocity curves for forced expiratory volume in 1 second (FEV_1) for boys (upper curves) and girls (lower curves). Solid lines indicate negative history of childhood respiratory illness; broken lines indicate positive history. From figure 1 of Borsboom et al. (20); reproduced with the permission of the American Lung Association.

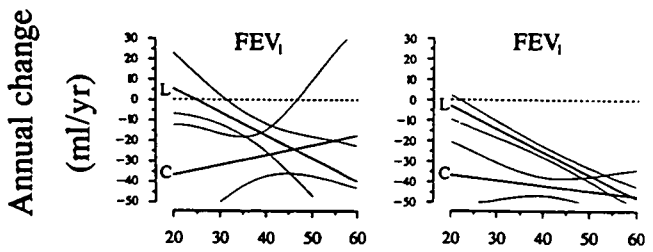

FIGURE 3. Annual rates of change in forced expiratory volume in 1 second (FEV_1) in female nonsmokers (left panel, n = 199) and smokers (right panel, n = 224). L = estimates based on pooled individual age-specific rates of decline; C = cross-sectional estimate of annual rate of decline. Thin lines are 95% confidence intervals around each line. From figure 3 of van Pelt et al. (19); reproduced with the permission of the American Lung Association.

heterogeneous growth patterns noted in figure 1. Finally, in a study of adults observed on at least three occasions over at least 9 years, the effects of cigarette smoking on lung function decline were evaluated with longitudinal and cross-sectional estimates. Several conclusions are evident from figure 3: 1) cross-sectional estimates of age-specific declines do not differ significantly between female smokers and nonsmokers; 2) longitudinal estimates show a more rapid rate of decline in smokers, especially in the youngest and oldest women; and 3) cross-sectional estimates exaggerate the rates of decline, especially in the youngest age groups.

The above series of studies clearly indicates the very different perspective that is provided by a longitudinal analysis compared with cross-sectional, population average estimates. In two instances (19, 21) the cross-sectional estimates lead to underestimates of effects at the individual level and, in one case, clearly misspecify the process of FEV_1 decline over time (19). With regard to issues of etiologic inference, the study on the effects of childhood respiratory illness on growth of FEV_1 (20) makes feasible an interpretation that would not have been as clearly evident from a purely cross-sectional analysis.

"Tracking," from an epidemiologist's viewpoint, relates to the tendency of an individual to retain his/her relative rank in a population distribution of some trait over time, or the ability to predict subsequent values of a trait from earlier values (23, 24). Studies of the natural history of blood pressure made extensive use of tracking analysis (25) and the concept of tracking underlies the use of "normal" growth charts (23). Clearly, such an approach is best served by multiple observations of subjects over time periods appropriate to the state of disease or health under consideration.

Segal and Tager (24) used a tracking analysis to determine the extent to which respiratory symptoms in

childhood influenced patterns of lung function development. Children aged 5–9 years at baseline who were studied annually for at least 5 years, and were at least 10 years of age at the final survey, were evaluated. Age-specific FEV_1 residuals were derived from a single underlying normal growth curve by the smoothing of all height-adjusted FEV_1 data (26). Figure 4 shows data for females in relation to whether or not they reported respiratory symptoms during the follow-up period. At all surveys, symptomatic girls had relatively lower levels of lung function compared with those without symptoms. Moreover, the relations between the groups remained relatively constant. These data are consistent with the hypothesis that symptomatic and asymptomatic children have different growth curves. Such differences in growth patterns might be useful as a risk marker for future susceptibility to chronic obstructive lung disease.

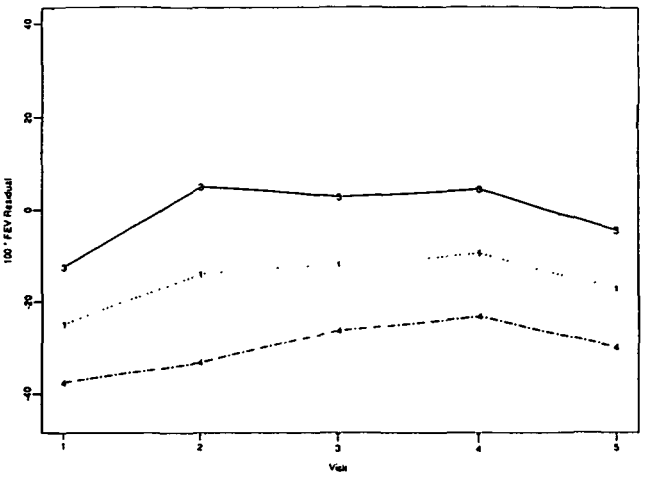

FIGURE 4. Height-adjusted forced expiratory volume in 1 second (FEV_1) residuals for female children aged 5–9 years at survey 1 who did or did not report respiratory symptoms during a 5-year follow-up. Line 1, all subjects; line 3, subjects without any respiratory symptoms; line 4, subjects with respiratory symptoms. From figure 3 of Segal et al. (24); reproduced with the permission of the publisher.

Estimation of the effects of risk markers over time on disease outcome

Often it is of interest to determine the relation between time-dependent changes in a marker of risk of disease onset (or onset of an altered functional state) and the occurrence of death in persons with disease. In the longitudinal cohort setting, the individual assessments of risk markers and outcomes at multiple time points all can be used to estimate an average population change in risk with change in exposure, and to evaluate individual heterogeneity in these associations.

A 1991 study from the National Cancer Institute (27) sought to define the relation between CD4 levels and death in 55 HIV-infected patients who were receiving antiretroviral therapy. Multiple CD4 determinations over time were available. The survival analysis included two different specifications for the possible time-dependence of the hazard of death and CD4 level: 1) a 0/1 indicator for whether the subject had 50 or more CD4 cells/mm^3 at each time of observation, and 2) another covariate that indicated the number of days since the CD4 count had fallen below 50 cells/mm^3. Thus, the authors were able to evaluate the hazard of death both as a function of the relative level of CD4 count at any give time of observation and estimate the additional impact of the time spent below the cutoff value. Obviously, this is a far richer set of inferences than would have been possible if just the baseline value had been used or some summary value created for the follow-up time.

Information on exposures, confounders, and effect-modifiers at the first observation of members of a cohort frequently can be viewed as imperfect surrogates for exposures of the subjects up to the time of inception of the cohort. Consequently, it is often desirable to estimate the effects of "baseline" (cross-sectional) characteristics on the outcomes in addition to time-dependent effects that might occur during the follow-up of the cohort which take into account individual-level changes. Two different approaches to this concept (18, 28), one of which makes use of a very efficient method for longitudinal analysis (18) in this context, will illustrate the points.

Congestive heart failure continues to be a major health problem, especially for the elderly (29); hypertension is the major risk factor for congestive heart failure (28). An 18-year follow-up of the Framingham cohort sought to investigate the ". . .natural history of the progression from hypertension to overt left ventricular dysfunction and an exploration of potential mechanisms. . ." (28, p. 1557). The principal outcome was development of new congestive heart failure. Two approaches were taken by the investigators: 1) a "static" Cox proportional hazards model considered only the hypertension status (and other risk factors) at the baseline evaluation, and 2) a "dynamic" proportional hazards model reassigned hypertension and other risk factor status at each evaluation; only reclassification to a higher risk category was considered, and this status was retained for the duration of the subject's follow-up time (table 4). The point estimates for the relative hazards and the upper bounds of the 95 percent confidence intervals were higher for the dynamic model, which reflects that fact that many subjects with normal blood pressure at the baseline evaluation subsequently developed hypertension with its attendant increase in

risk for congestive heart failure. Thus, an analysis that accounted only for the baseline hypertension status of subjects would have resulted in an estimate that was biased toward the null. However, individual differences in risk are not specifically accommodated.

Beckett et al. (18) sought to evaluate the effects of age and sex on levels of physical functioning in a 5-year follow-up study in the elderly subjects who were enrolled in the National Institute on Aging Established Populations for Epidemiologic Studies of the Elderly (EPESE). A random effects, mixed linear model (16) was used to evaluate the effect of age and sex at baseline and over the time of follow-up on the level of physical functioning at any given follow-up evaluation. The model also allowed for individual variation around baseline level of function and change per year from baseline. In this analysis, baseline age and sex can be interpreted as surrogates for cumulative effects of sex-specific aging and disease up to the inception of the cohort; the evaluation over time treats age and sex as surrogates for accumulation of sex-specific effects of aging over the period of follow-up. A graphic summary for one of the Rosow-Breslau measures (difficulty in walking [½] mile, climbing stairs, doing heavy housework) is presented in figure 5. As was the case for the study of peak growth velocities of FEV_1 (21), baseline estimate of change with age under estimates the changes observed over 5-year intervals for those who entered the study at different ages. Moreover, the fact that, at each of the ages for which longitudinal change in function score are shown, women declined more rapidly than men—an underlying process that is obscured in the cross-sectional (baseline) analysis. The authors also were able to estimate functional decline in those who died during follow-up, and confirmed that these subjects had both lower baseline function and a faster age-specific rate of decline.

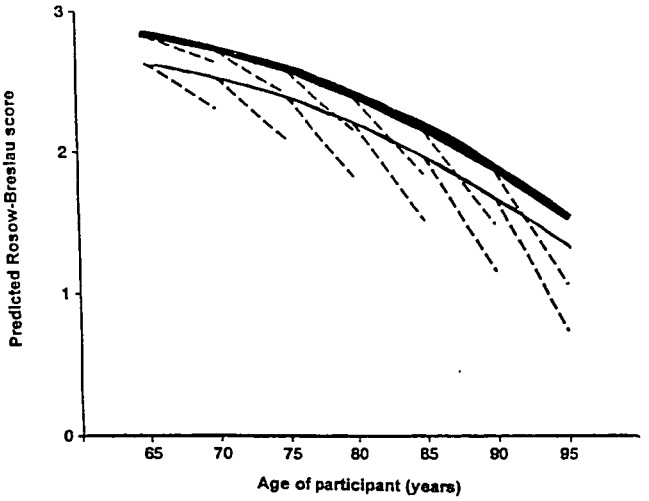

FIGURE 5. Predicted Rosow-Breslau scores and longitudinal changes by age and sex, Iowa component of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) population. Mean scores at baseline according to initial age (heavy line = men; thin line = women), and average decline predicted by model for men and women of a given age followed for 5 years (broken lines). From figure 1 of Beckett et al. (18); reproduced with the permission of the publisher.

Estimation of rate of change or change in level for outcomes that relate to disease natural history

Understanding of the occurrence of many diseases often entails a clear understanding of the behavior of anatomic, physiologic, biologic, and functional markers for a disease or state of health over time (table 2). Central to this process are quantitative descriptions of the normal patterns of maturation and decline of these characteristics, and how they might be influenced by exposures that are thought to be etiologic in the occurrence of a given disease or protective in the case of enhancement of health (e.g., physical activity). Such an approach to understanding disease and health has been a central feature of epidemiologic studies of the origins of chronic obstructive pulmonary disease (COPD), usually associated with cigarette smoking.

Patterns of growth and decline in measures of lung function have been an integral part of many hypotheses about the origins of COPD for many years (22). Only about 15 percent of persistent cigarette smokers develop COPD. One hypothesis to explain this heterogeneity of risk, the "Dutch hypothesis," suggests that an intrinsic hyperresponsiveness of the airways of the lung to noxious environmental stimuli is a critical risk

TABLE 4. Relation between hypertension and the onset of congestive heart failure (CHF) in the Framingham study (28)

Relative hazard* of CHF from static model†		Relative hazard of CHF from dynamic model†	
Males	Females	Males	Females
1.84 (1.35–2.51)‡	2.60 (1.77–3.81)	2.07 (1.34–3.20)	3.35 (1.67–6.73)

* Adjusted for age, angina pectoris, myocardial infarction, diabetes, left ventricular hypertrophy, and valvular heart disease.

† Data adapted from Levy et al. (28); see text for definitions of models.

‡ (95% confidence interval).

factor for the subsequent development of COPD in smokers (30). This risk is hypothesized to result in more rapid declines in lung function with age in those who are exposed and who are destined to develop the disease. Cross-sectional studies and cohort studies with only a few observations have not been able to test this hypothesis directly, since level of the risk factor (hyperactive airway response measured as a change in FEV_1 to a nonspecific pharmacologic stimulus) is, in part, determined by the level of the FEV_1 at the time of the measurement, which, in turn, is affected by cigarette smoking. To address this problem and to assure that the temporality of the environmental exposure (cigarette smoking) was correct in relation to the outcome (rate of decline in lung function), investigators analyzed data from a 25-year follow-up of several cohorts recruited to investigate the Dutch hypothesis (31). Annual change in FEV_1 between each survey (every 3 years) was calculated. This annual change was the outcome measure, and all exposures of interest were based on the values obtained at the first of any pair of consecutive surveys. Multiple methods of analysis were used to accommodate the repeated measures structure of the data and to evaluate the extent to which individual heterogeneity was an important factor. In all groups (based on smoking history) of subjects (table 5), those who had evidence of a hyperactive airway response had greater interval declines in FEV_1 compared with those who did not show this response. Moreover, in a separate investigation (32), the same authors were able to demonstrate that the within-subject variability of the measure of hyperresponsive airways was more stable over time than the variability between individuals that could be induced by losses to follow-up in the cohort, and uncontrolled period and age-cohort effects. Thus, the authors were able to provide what amounts to the first clear evidence that the trait of hyperresponsive airways does accelerate the decline in lung function and, thus, may explain, to some extent, why certain cigarette smokers develop COPD when others do not.

Additional support for the Dutch hypothesis can be found in a 12-year longitudinal cohort study of children aged 5–9 years at inception of the cohort (33). Children were studied annually. The authors used an autoregressive (transition) model (16, 34) to evaluate the level of lung function (maximum midexpiratory flow) at any given survey as a function of the lung function at the immediately previous survey and measures of height, change in height, smoking, and a measure of reactive airways. This transition approach does not evaluate rates of change directly; rather, it allows for a temporal description of growth that is based upon successive evaluation of the levels of lung function that accounts for immediate past history. Airways reactivity was associated with decreased levels of function at each survey, which suggested to the authors that airway reactivity could be a risk factor for environmentally-induced lung disease through an alteration of the normal development of the mechanical properties of the lung.

Clearly, the above inferences would not have been possible from either cross-sectional data or from a cohort study that used broad summaries of exposure that spanned long periods of time. The ability to directly evaluate the variability of the trait under study within individuals over time adds considerable strength to the Dutch hypothesis.

Natural history of states of health with multiple occurrences or that oscillate between states

As noted previously, life table-type cohort studies are limited to the study of single outcomes and, by

TABLE 5. Adjusted* difference in mean yearly change in forced expiratory volume in 1 second (FEV_1) between responders† and nonresponders† to histamine challenge, Vlagtwedde-Vlaardingen Study, The Netherlands (31)‡

Smoking status	Adjusted difference in yearly FEV_1 decline					
	Males			Females		
	No. of subjects	Adjusted difference	Standard error of the mean	No. of subjects	Adjusted difference	Standard error of the mean
Never	158	−12.2	(9.4)	511	−8.5	(4.2)
Former	464	−10.2	(5.6)	197	−14.1	(6.7)
Consistent	700	−7.6	(5.2)	317	−8.8	(5.3)
Other	287	−17.2	(7.1)	114	−10.5	(10.6)

* Adjusted differences estimated from multiple linear regression stratified by smoking habit and gender and with adjustment for age, residential area, respiratory symptoms, indicator for survey interval (period effects), and FEV_1 residuals at study onset.

† Responder to histamine defined as >10% decline in FEV_1 or inspiratory vital capacity to ≤16 mg/ml of histamine.

‡ Adapted from Rijcken et al. (31).

implication, cannot study diseases and states of health that can oscillate over time. The understanding of the complex behavior of disease states or various states of health often depends on the ability to account for the previous history of individuals in relation to their current status and in relation to a particular outcome.

As part of the study on the effects of age and sex on levels of physical functioning in the elderly noted above, Beckett et al. (18) sought to evaluate the transitions between states of disability (self-reported inability to perform an activity on several standard inventories) and no disability. One Markov (transition) model evaluated the probability (logistic function) of transition from no disability to disability, and another model evaluated the probability of transition from disability to no disability. For example, the authors observed that males were significantly less likely than females to report a new disability, and more likely to report recovery from most disabilities. Figure 6 (from Beckett et al. (18)) shows the estimated transition probabilities to disability versus age for the Rosow-Breslau measures for men and women who did and did not survive for the duration of the study. At each age, men, regardless of their survival in relation to the study, were less likely than females to become disabled as they aged.

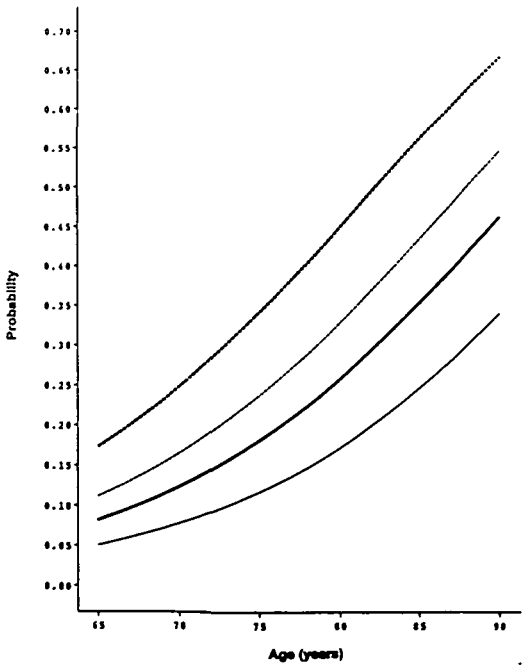

FIGURE 6. Estimated transition probabilities to disability (Rosow-Breslau scale, Iowa component of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) population). Heavy solid line = women who survived the entire study, heavy broken line = women who died before the end of the study; light solid line = men who survived the entire study, light broken line = men who died before the end of the study. From figure 2 of Beckett et al. (18); reproduced with the permission of the publisher.

Hilton et al. (35) examined the risks for oral candidiasis and hairy leukoplakia persons whose HIV infection occurred as the result of blood transfusion or therapy for hemophilia to determine if the two groups differed in their risks for these oral lesions that are associated with HIV infection. Since oral candidiasis is a recurring and remitting lesion, a transition model approach was used (16). Data were available for 154 subjects and 1,087 oral examinations (examinations were 3- or 6-monthly). The odds of oral candidiasis at any given examination were found to be increased if candidiasis was present at the visit immediately prior (odds ratio = 8.8), two visits prior (odds ratio = 3.76) and both visits prior (odds ratio = 9.62 (8.82*3.76*0.29)) to a current examination. Markers of immune status (CD4:CD8 ratio and log CD8 count) and presence of hairy leukoplakia also affected the odd ratio (table 6). However no evident effect was observed for the comparison between all transfusion recipients and hemophiliacs.

Although both of these studies have used the longitudinal structure of their data to focus on transitions between various states health, they have approached the problem somewhat differently. Beckett et al. (18) chose to separate the description of transition from nondisability to disability from the reverse process and to derive their inferences through a comparison of the two models (18, tables 7–9). In contrast, Hilton et al. (35) used a single model to evaluate the effect of prior disease status on current status, which permitted the evaluation of an interaction term for disease status at the two prior visits. This permitted direct estimation of the extent to which past persistent oral candidiasis influenced current risk. In the approach taken by Beckett et al., the effect of duration of reported disability could not be evaluated on the odds of recovery.

Separation of cohort or period effects from the effects of age or calendar time

Life table-type cohort studies clearly can identify cohort or period effects which, if unrecognized, clearly could bias estimates of effects that are attributed to age or the passage of calendar time. Figure 7, taken from the 1982 report of the Surgeon General on the relation between cigarette smoking and cancer (36), shows the now well-recognized relation between birth cohort and lung cancer in males that is attributable to the epidemic of cigarette smoking that began near the turn of the 19th century and rapidly accelerated during the time of World War I. Although the data in figure 7 did not come from a specific cohort study, such data easily could have been developed from the British Doctors Study cited previously (11). Repeated measures cohort

TABLE 6. Odds ratios for the occurrence of oral candidiasis in human immunodeficiency virus-positive transfusion recipients, San Francisco Bay Area, 1985–1993 (35)*

	Odds ratio	95% confidence interval
Intercept	0.92	0.19–4.52
Oral candidiasis, 1 prior visit (OC1)	8.82	4.84–16.1
Oral candidiasis, 2 prior visits (OC2)	3.76	1.97–7.18
Oral candidiasis, 3 prior visits (OC3)	†	
OC1 and OC2	0.29	0.11–0.78
CD4:CD8 cell ratio	0.21	0.10–0.45
Log CD8 cell count	0.77	0.61–0.99
Hairy leukoplakia at current examination	3.28	1.83–5.88
Transfusion recipient versus hemophiliac	‡	

* Adapted from model 2 in table 3 of Hilton et al. (35). Model 2 was the second of three models that were developed in sequence to evaluate successive contributions of the factors: italicized variables were included in model 1, normal type variables were included and were added to model 1 variables to create model 2.
† Not statistically significant in model 2; odds ratios 1.76 (95% confidence interval 1.02–3.05) in model 1.
‡ Not statistically significant.

studies permit the separation of cohort or period effects from age effects for processes that may change over time in individuals. Although the inferences from such analyses are more in the spirit of population average effects, their estimation would not be possible without repeated measures on individuals over long enough periods of time.

Another analysis from the Vlagtwedde/Vlaradingen cohort (31) that was based on 24-years of follow-up sought to disentangle the effects of age and period from age-related declines in lung function with age among individuals with different smoking histories (37). Age and period effects were evaluated separately due to the linear dependence between age, period, and cohort (38). Only the age cohort part of the analysis is summarized. Subjects who were surveyed every 3 years were included in the analysis if they were born between 1911 and 1949 and had stable smoking habits (reported as "never," "current," or "former" at baseline and all follow-up evaluations). The regression model to separate age effects from cohort effects included terms for age, age^2, birth cohort (four cohorts), and an age*cohort interaction to evaluate whether age-related declines in lung function differed by cohort. The age coefficient in this model was interpreted by the authors as the "longitudinal" age effect on lung function (average population average individual rates of decline in FEV_1), since the coefficient estimates the effect of age, with the cohort fixed (37). The within-subject correlation between successive measures of lung function was accounted for in the analysis. Figure 8 demonstrates that, in males, cohort effects are blunted in smokers relative to those observed in never smokers and former smokers. The interaction between age and cohort was not significant. In females, cohort effects for former smokers resembled more those of current smokers, and the cohort pattern of decline for non-smoking females resembled that for males, except for less steep change with age. The difference in the cohort patterns between the men and women could be explained by the differences in the epidemic of smoking in males and females. The epidemic occurred earlier and peaked earlier in males (36). Thus, men

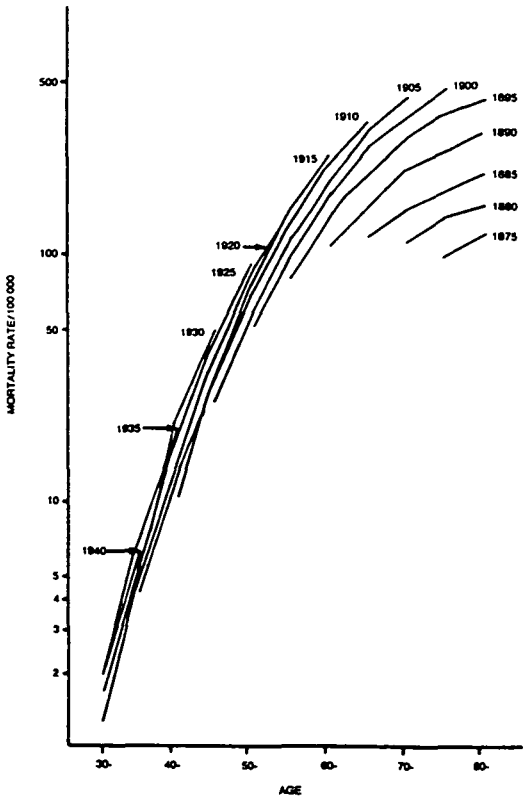

FIGURE 7. Age-specific mortality rates from cancer of the bronchus and lung by birth cohort and age at death for males, United States, 1950–1975. From *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (39, p. 52).

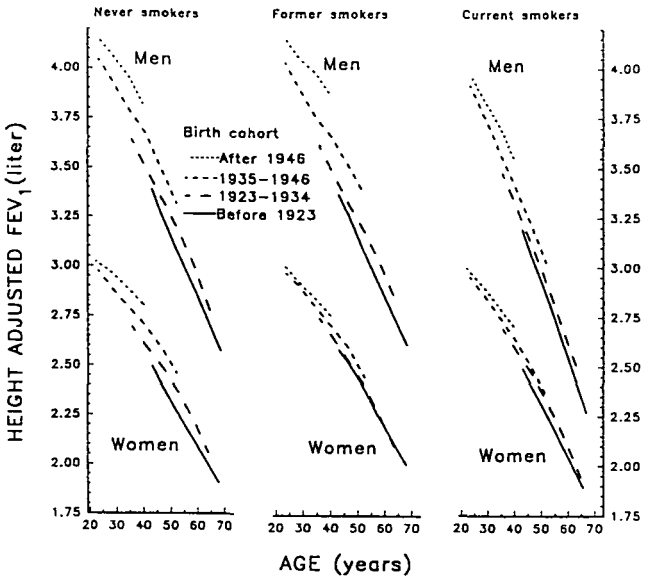

FIGURE 8. Height adjusted forced expiratory volume in 1 second (FEV_1) for males and females in the Dutch Study on Asthma and Chronic Obstructive Pulmonary Disease (1965–1990) by smoking status and birth cohort for subjects with the same smoking status at all surveys. From figure 2 of Xu et al. (37); reproduced with the permission of the publisher.

who were former smokers may have quit for a longer period of time then their female counterparts.

CONCLUSION

Longitudinal cohort designs clearly offer the opportunity to explore a wider range of processes and outcomes that are of major interest to epidemiologists. They offer the means to explore the natural history of the biologic, social, and environmental processes that are important determinants of disease occurrence and preservation of health in a manner that is not possible with life table cohort-type designs or case-control studies. Moreover, advances in statistical methodology for longitudinal data (16), and the wide availability of software to implement these methods, make it feasible to ask a wider range and complexity of questions in the context of epidemiologic cohort studies than would have been feasible in the past.

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