METHODS AND ANALYSIS ISSUES IN LONGITUDINAL STUDIES OF GROWTH

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1. Introduction

In longitudinal studies, data for one or more variables are recorded at more than one point in time. Follow-up studies constitute a special class of longitudinal studies in which there are only two examinations for each subject. While many longitudinal studies, such as those related to human growth, extend over years or decades, those concerning physiological variables, for example, the concentrations of blood gases, may be of brief duration but yet include many data points for each individual.

Longitudinal studies can provide information that cannot be obtained from cross-sectional studies; therefore, they have considerable appeal to research workers. Nevertheless, the unique potential of longitudinal studies will be achieved only if appropriate statistical analyses are made. It may be difficult to translate the results of these analyses, which are often complex, into clinically applicable findings or to use them in formulating public policy. The statistical analyses needed for cross-sectional studies are generally simpler to perform and the results can be easily explained and applied with less concern as to whether they are suitable for a general population. For these and other reasons, cross-sectional studies should be preferred if the questions addressed to not relate to changes within individuals.

The emphasis in this account will be on long-term serial studies of human growth. These studies, more than most, require careful planning because they are expensive and because most are multidisciplinary. If not multidisciplinary, at least, many variables should be recorded while unusual opportunities exist to relate present and previous data for individuals. There have been about seven longitudinal growth studies in the U.S.of which only The Fels Longitudinal Study remains active in enrollment, data collection and data analyses.

Planning for such a study is tedious. This planning should begin with the establishment of short-term and long-term aims. Short-term aims are necessary for some research topics, to obtain funding, and to recruit professional staff, although the long-term aims may be of greater interest.

The study may be based on the enrollment of one cohort or of annual cohorts at one or more specified ages, usually birth or 6 years when grade school begins. In either case, repeated measurements may affect the phenomena being measured. Problems resulting from this can be avoided by choosing a design that allows the separation of age and examination effects, as has been done for auditory thresholds (Roche et al., 1983). The possibility of such an analyses will occur whenever a measurement procedure is added to the protocol, in a particular calendar year, to be applied to participants of various age.

The design of the Fels Longitudinal Study is shown diagrammatically in Figure 1. Annual cohorts have been enrolled since 1929, except for a hiatus from 1975 through 1982 for financial reasons. The resultant data base, from more than 1,000 subjects, provides many analytic possibilities. Working with this data base is fun; doubly rewarding because it is fun with a purpose.

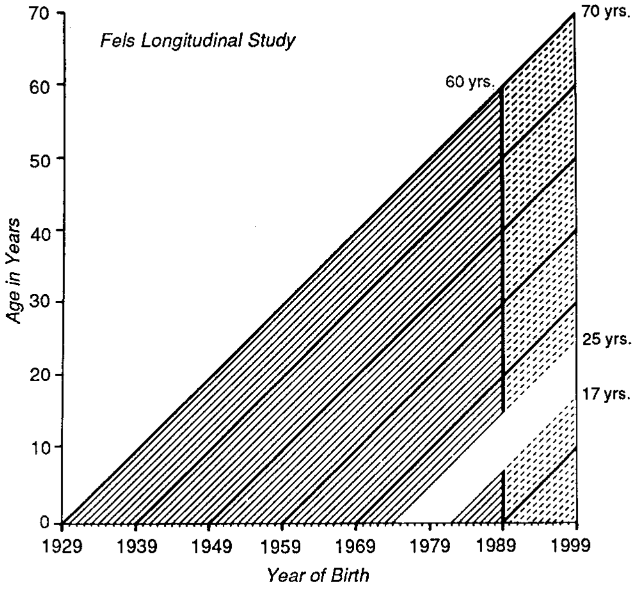

Figure 1. The design of The Fels Longitudinal Study.

There may be concern about possible secular changes within such a data set. These changes can be of several types. There may be differences in size or in growth patterns between a single cohort, enrolled perhaps 40 years ago, and the cohorts enrolled recently. This hypothesis can be tested for size but not for long-term growth patterns, for example, 2 to 18 years, because data are necessarily lacking for the children enrolled recently. Hypotheses regarding secular changes in size or in growth patterns can be tested within a study based on annual cohorts by regressing measured values or parameter estimates against year of birth or by comparing birth year groups (Kouchi et al., 1985a, b). Such analyses refer to the total sample. The Fels design also allows analyses of data from participants of like sex but different generations within families (Bock et al., 1985). It could be hypothesized that secular changes occur in the associations between the patterns of change in two variables, e.g., total body fat and blood pressure. Serial data from annual cohorts allow such a hypothesis to be tested.

Having enrolled participants into a longitudinal study, it is essential to retain them . All the study staff must make great efforts to ensure that the examinations are as pleasant and convenient as possible. Gifts, newsletters and Christmas cards help to reduce attrition and continuity of the contact staff is very important. The annual attrition rate can be as low as 1 in 600 but it cannot be reduced to zero. Hypotheses that those who withdrew were representative of the total sample at their last examinations can be tested. It is possible also to test whether the omission of the data recorded at their last examinations affect the calculated relationships between variables and whether those who withdrew differed from the total group in their preceding growth patterns.

2. Design Considerations

The design considerations for a longitudinal study include the characteristics of the participants, sample size, the selection of variables, arrangements for data collection and quality control, data base management, and data analyses. All these must be fully documented. The selection of participants and of variables will be determined largely by the aims of the study but some general principles apply to all longitudinal studies. The sample size should be based on power calculations for the most important analyses to be made. The data collection procedures should be non-invasive and painless. The group of procedures applied at any one visit should not require excessive time or cause the participants excessive fatigue. Ideally the procedures should be applicable in a clinic or in the field, but, if this is impossible, sets of other variables should be recorded that allow values to be predicted for tests that require complex laboratory equipment.

All variables should be measured using the best procedures and equipment; these should be changed as improvements become available. When there is such a change, overlapping observations should be made using both the old and the new procedures and equipment to establish the relationship between the two. Such changes should be made cautiously in agreement with the dictum of Alexander Pope:

> "Be not the first by whom the new are tried,
> Nor yet the last to lay the old aside."

Longitudinal studies are appropriate milieux for testing new procedures, but, in general, different participants should be used for these studies which are likely to be cross-sectional or short-term longitudinal.

If the study has focused aims and appropriate variables are chosen, there will be many interrelationships between the variables. Analyses of these interrelationships may lead to better understanding of the research topic and lead to a recognition that further variables should be added. Variables should not be added just because they are interesting.

The intervals between examinations should be shorter when growth is rapid and when inflections in growth rates are expected than at other ages. A schedule on this basis will be suitable for all growth variables except those relating to the craniofacial area which grows very rapidly during infancy but has only small pubescent spurts.

Data quality is important in a cross-sectional study because systematic and random errors affect the distributions. In a longitudinal study, these errors will have corresponding effects but, in addition, they alter the recorded patterns of change for individuals. Therefore, excellent data collection procedures are essential in a longitudinal study. The measurement techniques for variables related to growth should match consensus recommendations (Lohman et al., 1988) and be made by two well-trained anthropometrists working independently. Entry of the recorded data to a computer, while the participant is present, allows checks of inter-measurer differences and of accuracy relative to reference data and to the data recorded at the previous examination of the participant. These checks can lead to re-measuring. The data should be placed in a separate computer file until they have been checked against the hand-written records. Only after data entry errors have been corrected, and the corrections checked, should the data be entered to the data base file.

3. Selected Analyses From The Fels Longitudinal Study

a. Follow-up studies. Pairs of data points were used to estimate the risk of overweight (> 75th percentile for sex) at 18 years based on weight during childhood. Regression analyses of weight during childhood on weight at 18 years showed the coefficients of variation (CVs) were similar in each sex. These values decreased in a near linear fashion, with slight increases during pubescence, as older childhood ages were considered (Figure 2). Percentile status during childhood was determined from national reference data (NHANES II) and the participants were placed in 6 groups (> 10, 10-25, 25-50, 50-75, 75-90, > 90 percentile). The probability of being overweight at 18 years was estimated from percentile levels during childhood using a logistic function (Figure 3). The fit was good except for the group below the 10th percentile. Commonly, a higher proportion of the group below the 10th percentile became overweight than was the ccase for the group between the 10th and the 25th percentiles. The logistic function was used to estimate odds ratios and log odds ratios; both these sets of ratios differed little among percentile groups until 3 years of age and older.

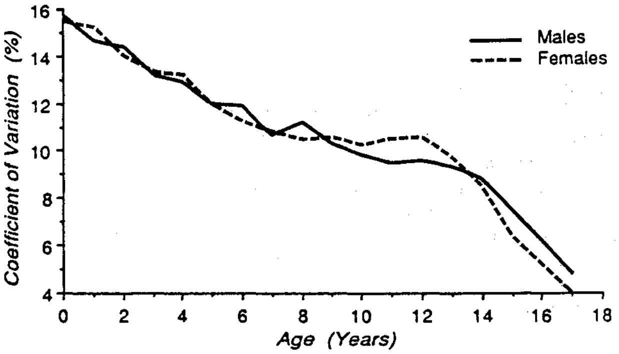

Figure 2. Coefficients of variation from regressions of weight during childhood on weight at 18 years in boys.

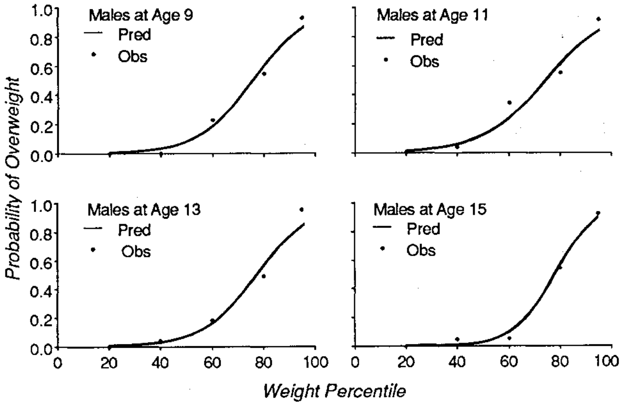

Figure 3. Fits of a logistic function to the probabilities of overweight at 18 years for percentile groups in regard to weight at selected ages in boys.

Figure 4 shows these ratios for the upper percentile groups. The risk was greater for those above the 90th percentile than for those between the 75th and 90th percentiles for childhood weights in each sex. For corresponding groups, the risk tended to be greater for males than for females, except after 14 years. Corresponding analyses have been made with weight/stature^2 as the dependent variable and with the dependent variables at 30 years.

In another analysis pairs of serial data points were used to obtain reference data for increments in growth variables.

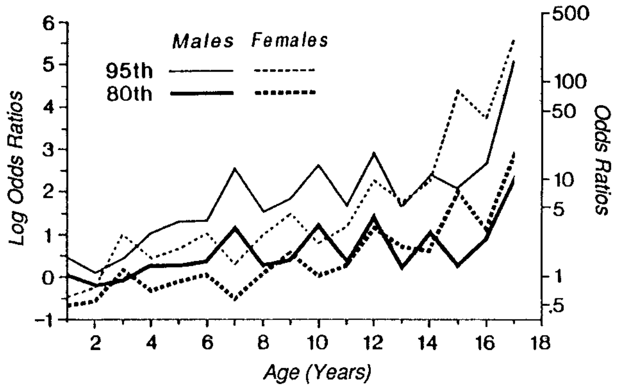

Figure 4. The odds and log odds ratios for risk of being overweight (> 75th percentile) at 18 years based on childhood weight percentiles.

Increments were calculated between values 6 months apart for several variables from birth to 18 years (Roche and Himes, 1980). The smoothed empirical percentiles for these increments were presented as reference data for clinical use in monitoring the growth of individuals and to assist research relating to groups. As an example, percentiles for weight increments from birth to 3 years in boys are shown in Figure 5. A rapid deceleration is evident particularly for the upper percentiles. Cross-sectional data can provide increments between means or medians but only longitudinal data can provide the distributions of these increments.

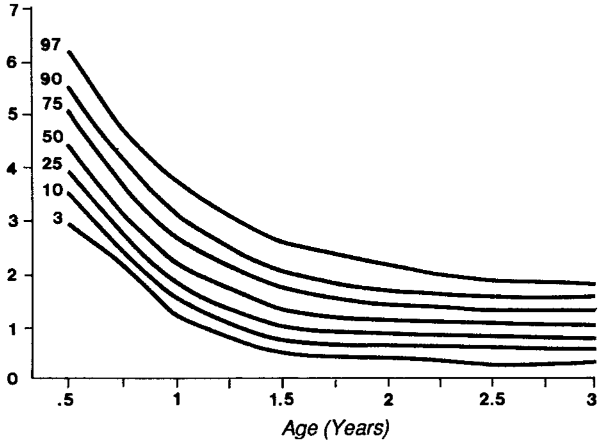

Figure 5. Reference data for 6-month increments in weight for boys. (Reprinted with permission from Am. J. Clin. Nutr. 1980, 33, 2041-2052).

b. Modelling serial data. Fitting mathematical models to serial data for individuals can serve several purposes. One purpose is interpolation within the age range of the data. This was done in one analysis of Fels data for weight during infancy (Roche et al., in press). There is a clinical need for growth increments during 1-month intervals for infants, but few studies have a sufficient number of infants measured at these intervals. Accordingly, clinicians have been forced to use reference data for 3- or 6-month increments or to judge rates of growth from changes in percentile levels for status at various ages.

In The Fels Longitudinal Study, infants were measured 5 times during the first year of life and at 18 and 24 months. The following 3-parameter model was fitted to the serial data for each infant.

$$f_i\,(t_j) = a_i + b_i\sqrt{t_{ij}} + c_i \log t_{ij} + e_{ij}, \qquad (1)$$

where fi (tj) is the measurement (kg) of the ith infant at age t_j (years), a_i, b_i, and c_i are the parameters, and e_{ij} is an error term.

After it had been shown that the fit was good in each infant, the model was used to estimate values for weight at each month of age from 1 to 12 months. Increments between these values were calculated and selected percentiles of these increments were presented graphically for clinical use. Those for boys are shown in Figure 6.

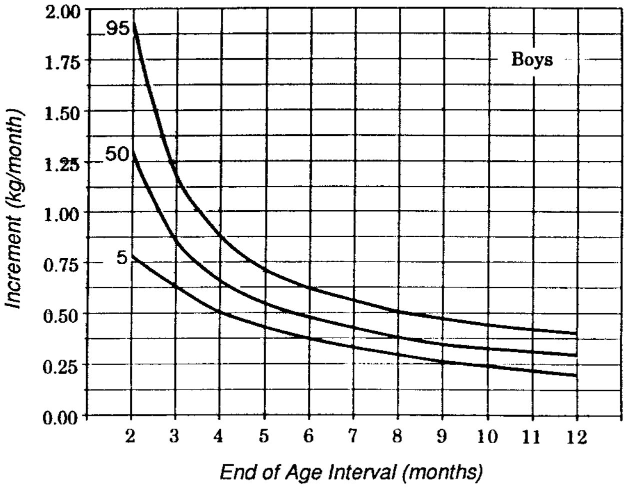

Figure 6. Reference data for 1-month increments in weight for boys during infancy.

Associations between the patterns of growth for two variables can be studied using correlations between the parameters of models fitted to the serial data for each variable. This is appropriate if it is biologically reasonable to hypothesize such an association and if the parameters of the model are interpretable. Such an analysis has been made using Fels data for weight and recumbent length during infancy (Kouchi et al., 1985a, b). The model was:

$$f_i(t_j) = \theta_{1i} + \theta_{2i} t_{ij}^{\theta_{3i}} + \varepsilon_{ij} \qquad (2)$$

where f_i (t_j) was the measurement (kg or cm) for the ith infant at age t_j (years) and $(\theta_{ij}, \theta_{2j}, \theta_{3j})$ was a vector in the parameter space for the ith infant and ε_{ij} was an error term. This model was fitted to weight from birth to 24 months and to recumbent length from 1 to 24 months. In each sex, $\hat{\theta}_1$ was the asymptotically estimated value at birth, $\hat{\theta}_2$ was the intrinsic rate of growth and $\hat{\theta}_3$ was a dimensionless parameter which chracterized the shape of the curve. If $\hat{\theta}_3 = 1$, then the model is linear and if $\hat{\theta}_3 > 1$, the curve is concave upward.

Such an approach can lead to further analyses of the parameters that may be related to possible secular changes or associations between the patterns of growth for two variables. The parameters of models can be used also to calculate intrafamilial correlations. Those for recumbent length in Table 1 are based on measurements of different family members at matching ages. The parent-offspring correlations are not significant but most of those for sibling pairs are significant.

Table 1. Intrafamilial correlations for the parameters of equation (2) applied to recumbent length (1 to 24 months).

		θ_1		θ_2		θ_3	
Pairs	N	r	s.e.	r	s.e.	r	s.e.
Parent-offspring	80	0.21	0.11	0.13	0.11	0.06	0.11
Sib-sib	282	0.37**	0.06	0.38**	0.06	0.16	0.06
Brother-brother	96	0.48**	0.10	0.32**	0.10	0.18**	0.10
Sister-sister	97	0.38**	0.10	0.37**	0.10	0.21*	0.10
Brother-sister	151	0.36**	0.08	0.43**	0.08	0.15	0.08

* = $p < .05$; ** = $p < .01$.

4. Modifying The Design

Attention to design is essential when planning a longitudinal study and during all the time it continues. The emphasis of the study is likely to change as particular topic areas alter in the opportunities they provide for research, but the changes should be gradual so that a balance is kept between the original aims of the study and later modifications to these aims. If this is done, all the data recorded early in the study will be useful for the analyses made late in the study. Completely new topics may emerge. If these topics are added to the design and they are not related to the original aims, the variables recorded earlier will probably be irrelevant.

This paper uses the long-term study of human growth as an example to illustrate methods, analyses and design issues in longitudinal studies. It could be claimed that such studies should end when the subjects are 18 years old. This has been the common pattern. The research potential of a growth study is not achieved, however, when the subjects reach the age of 18 years. The examinations should continue but should be separated by longer intervals. The questions addressed will alter and may relate to risk factors for disease and to diseases themselves, partly in relation to childhood growth patterns. Intergenerational data may become available and studies of changes during middle and old age, in relation to childhood variables, will become possible. It has been stated as a truism that man cannot perform a serial study of human beings throughout their life spans because the investigators will not live long enough. Nevertheless, this can be achieved by a succession of investigators each using the same procedures. Unusual sets of data can be obtained, such as those for annual increments in recumbent length and stature from 1 to 56 years (Roche et al., 1981).

5. Conclusion

This overview emphasizes some principles underlying the design and management of long-term growth studies. The statistical procedures that should be applied will differ, of course, depending on the specific nature of the data set and the hypotheses to be tested. It is hoped that the examples described provide convincing evidence of the need to apply proper statistical techniques in longitudinal data analyses.

Acknowledgement

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