Comment

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We find ourselves in substantial agreement with the authors on most of the issues raised in the paper. This makes criticism difficult, so our comments are restricted to two points, namely, the role of marginal regression models in applied work and the role of the so-called robust variance estimator of empirical sandwich variance estimator.

MARGINAL REGRESSION MODELS

The purpose of this note is to comment on the role of marginal regression models in the context of longitudinal studies. The authors' arguments are presented in terms of parameter interpretation or "reproducibility," or what McCullagh and Nelder (1989) in a similar context call "upward compatibility." In the marginal model, one focuses primarily on a model for the marginal mean vector. In a fully specified model, the focus is usually on the conditional distribution of the response at time t given the observed history of that individual on previous examinations.

Most studies have multiple purposes, some specified in advance, others after the fact. We take the view that, in general, the choice of model must depend not just on the nature of the variables and the choice of design, but also on the purpose of the study. Different questions usually require different models to be fitted to the same data. Some purposes are well served by a sequence of conditional models given the individual's history: other purposes are better served by a marginal regression model. The megalomaniacal strategy of fitting a grand unified model, supposedly capable of answering any conceivable question that might be posed, is, in our view, dangerous, unnecessary and counterproductive. It violates that basic principle of applied statistics, the avoidance of unnecessary modelling.

For present purposes, it is helpful to consider purposes of medical investigations in human subjects under four headings:

(i) Scientific understanding;
(ii) Clinical prediction;
(iii) Public policy decisions;
(iv) Epidemiological purposes.

A major distinction is immediately apparent in that purposes (i) and (ii) focus on the individual, whereas (iii) and (iv) focus on the population, however defined. Purposes (i) and (ii) are therefore best served by an individual-specific model focusing on the conditional distribution of an individual's disease status given the relevant past history for that individual. Purposes (iii) and (iv) are more directly served by a marginal regression model in which population rates or averages are the primary parameters under study.

The following simplified example serves to illustrate how the purpose of a study can have a drastic effect on model choice and parameter interpretation. Consider a study set up to investigate the effect of mother's smoking habits, X_1, on infant perinatal mortality, Y. Any such study will, as a matter of course, collect information on a large number of variables, many of which have little bearing on the advertised purpose of the study. For present purposes, we consider only two other variables, namely, age of mother X_2 and duration of pregnancy Z. Some of these variables may be discrete, others continuous. For example, Z might be measured in days (essentially continuous), or it might be an indicator for premature birth, however defined. Measurement scales, however, are irrelevant to the discussion that follows. Duration of pregnancy has the status of an intermediate variable, temporally subsequent to X_1, X_2, but preceding the ultimate response Y. In the trivariate regression of Y on X_1, X_2, Z, duration of pregnancy is by far the most effective predictor of perinatal mortality. Premature babies have a much higher mortality rate than full-term babies. Smoking habit of the mother has little additional predictive power. Whether or not it has a causal interpretation suited to purpose (i), this trivariate regression model is the model of choice for clinical prediction.

From a public-policy perspective, however, the conditional mortality rate given duration of pregnancy is of little interest. It is a plausible supposition that the major effect of smoking occurs in utero, reducing the duration of pregnancy and increasing the proportion of premature births. The direct perinatal effect of smoking during the week following birth is likely to be small. Smoking kills, but only slowly. In the regression of Y on X_1, X_2, Z, the major effect of increased tobacco consumption may be masked by a consequent reduction in duration of pregnancy. It is, of course, the total effect of smoking on perinatal mortality that is chiefly of interest for public health policy purposes. For that purpose, the marginal regression model of Y on X_1, X_2, omitting the intermediate variable Z, is required. In the absence of interaction with age, the coefficient of

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