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Sharon Xiangwen Xie Ph.D., Assistant Professor of Health Evaluation, Penn State University Sciences. is the recipient of the SIE **Young Investigator Award** at the 1999 ASA Meedings, This $500 award is given to the investigator less than five years past their terminal degree who submits the best paper for presentation at a session sponsored by the Statistics in Epidemiology section at the Joint Statistical Meetings.

Sharon received her Ph.D.from the University of Washington, 1997 During her graduate work, she collaborated with clinicians/scientists in the areas of HIV/AIDS research and Laboratory Medicine. She studied the anitbody production for HIV early infection patients and the variability of local antibody sampling. As part of her doctoral thesis, she developed new methods for estimation of the relative risk parameters in failure time regression when there is measurement error in the covariates (e.g. fat intake). Dr. Xie's statistical interests are in the areas of survival analysis, measurement error/missing data problems, longitudinal data analysis, and clinical trials.

Cost-Effectivenes Analysis

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Cost-effectiveness analysis (CEA) is an evaluation methodology that can be used to compare the costs and outcomes of different health promotion interventions or medical treatments. The results of a CEA are typically represented by one or more cost-effectiveness (CE) ratios. Each CE ratio is the difference in costs between two interventions, divided by the difference in intervention effectiveness. The CE ratio is thus a measure of the incremental costs and effects of one intervention, relative to another.

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Hierarchical Modeling in Epidemiology

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Epidemiologic investigations routinely collect large amounts of information. The measures (or estimates) resulting from analyzing these data often have some relevant similarities. For example, in cancer mapping, one might use data from a cancer registry to estimate standardized incidence rates for particular cancers across numerous geographic areas; similarities between these estimates include cancer type, geographical location, and the calendar time during which cancer occurred. Conventional estimation generally ignores the additional information provided by such similarities, and must deal with problems of multiple comparisons (1). The latter

problem arises from performing numerous analyses on the same data without taking into consideration the increased likelihood of falsely detecting an association. The suitability of suggested solutions to this problem, which include "correcting" the resulting estimates for having made multiple comparisons, have been extensively questioned (see, for example, Witte et al. (2)).

Hierarchical modeling—incorporating higher level "prior" models into a conventional analysis—offers a solution to problems of multiple inference. Furthermore, this approach can give estimates that are more plausible and stable than conventional estimates by "borrowing information" from the similarities in one's data. For example, in cancer mapping, standardized incidence or mortality rates may be improved by using a spatio-temporal second-stage model to pull estimates toward each other when they are close in location and calendar time. Based on the theoretical and applied work to date, the potential benefits of using hierarchical models are considerable (3-7). However, surprisingly few epidemiologic investigations have applied hierarchical models (8-10). Therefore, I present here some of the theory and methods underlying hierarchical modeling, and examples of how one might apply this approach in epidemiology.

Hierarchical models

Assume that one collects data on multiple correlated exposures of interest **x** (say, food intake), and disease status y. Further assume that one wants to use these data to estimate coefficients β for the effects of these exposure on disease. One can estimate β from the following generalized linear model for the expectation of y conditional on **x**,

$$g_1[E(\mathrm{y}|\mathbf{x})] = \alpha + \mathbf{x}\beta, \qquad (1)$$

where g_1 is a monotonic differentiable strictly increasing link function between the random and systematic components, and y has mean E(y|**x**) and variance σ^2. Conventional analytic approaches to estimating β using equation 1 include: 1) fitting a (full) model that contains all of the exposures; 2) reducing a full model with a preliminary testing algorithm (e.g., stepwise); and 3) constructing numerous one-at-a-time models (i.e., evaluating the multiple parameter inference problem as multiple one-parameter inference problems) (7). Unfortunately, none of these approaches provides entirely satisfactory estimates of β. Approach 1 is impractical if the parameters are non-estimable (i.e., too many parameters for the amount of data); moreover, even when the parameters are estimable, this approach can give biased and inefficient estimates. Approach 2 excludes statistically "non-significant" exposures from the full model regardless of their biologic importance (11, 12), and produces biased point and variance estimates (3, 4, 13). Approach 3 takes no account of correlations among the exposures. Finally, none of the approaches properly address issues of multiple comparisons (4, 14).

Instead of undertaking a conventional analysis, one can use a hierarchical model to estimate β. This approach provides a coherent framework for multiple inference problems, using shrinkage estimation to improve estimation accuracy (3, 6). In particular, this approach uses higher level "priors" to model the parameters of interest (here β) as random variables whose joint distribution is a function of hyperparameters. Assume that in addition to the above data (i.e., **x** and y), one has information about similarities between the components of β. For example, Witte et al. (6) estimated the effects of 87 foods on breast cancer. Similarities among these foods included their nutrient composition. One can use such additional information in a second-stage generalized linear model for the expectation of β conditional on this information,

$$g_2[E(\beta\ |\mathbf{Z})] = \lambda + \mathbf{Z}\pi, \qquad (2)$$

where g_2 is a strictly increasing link function, β has mean E(β |**Z**) and variance τ^2, and **Z** is a second-stage design matrix expressing the similarities between the β. For example, in the diet and breast cancer example (6) a linear link function we assumed, and a second-stage design matrix **Z** was defined where z_{ij} indicates the level of nutrient i in food j. Thus, the coefficients for each food effect β_i could have distinct second-stage means (the λ_i), but would also be related through a second-stage covariate (i.e., their nutrient composition) that is thought to be relevant to the strength of the food specific effects (which are measured by β_i).

Hierarchical (i.e., posterior) estimates are then obtained by combining results—in the simplest sense essentially taking weighted averages—from the different level models. Weights used in combining these results reflect how well each stage was able to estimate that level's parameters. Specifically, more unstable

estimates will be given smaller weight, and vice-versa. Hence, if sufficient data exist to estimate adequately first-stage parameters, adding a second-stage will have limited affect on these estimates. To fit the separate levels in a hierarchical model one can use iterative weighted-least-squares. Assume that one has conventional maximum-likelihood coefficient estimates $\hat{\beta}$ from fitting a first-stage model. One can then compute hierarchical estimates $\tilde{\beta}_W$ of the coefficients β by averaging $\hat{\beta}$ with the fitted E(β) from the second-stage regression of $\hat{\beta}$ on **Z**. In particular, one can estimate the second-stage regression coefficients π using weighted-least-squares:

$$\tilde{\pi} = (\mathbf{Z'WZ})^{-1}\mathbf{ZW}\hat{\beta}, \quad (3)$$

where $\mathbf{W} = (\hat{\mathbf{V}} + \mathbf{diag}(\tau^2))^{-1}$, and $\hat{\mathbf{V}}$ is inverse information for β evaluated at $\hat{\beta}$. The fitted value for β from the second-stage regression is therefore $\mathbf{Z}\tilde{\pi}$. Averaging $\mathbf{Z}\tilde{\pi}$ with the maximum-likelihood estimates β gives the hierarchical estimate

$$\tilde{\beta}_W = \mathbf{BZ}\tilde{\pi} + (\mathbf{I} - \mathbf{B})\hat{\beta}, \quad (4)$$

with estimated covariance matrix

$$\tilde{\mathbf{C}} = \hat{\mathbf{V}}[\mathbf{I} - (\mathbf{I} - \mathbf{H})'\mathbf{B}] \quad (5)$$

where $\mathbf{B} = \mathbf{W}\hat{\mathbf{V}}$, **I** = identity matrix, and **H** = $\mathbf{Z}(\mathbf{Z'WZ})^{-1}\mathbf{Z'W}$. Equation 4 shows how two-stage hierarchical modeling compromises between first- and second-stage estimates: the distance of the hierarchical estimate from the estimates in either stage is indirectly proportional to the stability of the stage-specific estimates. More specifically, the larger the elements in $\hat{\mathbf{V}}$ are, the further $\beta_{\mathbf{W}}$ will be from $\hat{\beta}$. Conversely, the larger the τ^2 are, the further $\beta_{\mathbf{W}}$ will be from $\mathbf{Z}\tilde{\pi}$.

Using the weighted-least-squares approach requires that enough data exists to estimate the parameters in a full first-stage model. When this is not the case, a penalized likelihood hierarchical approach can be used instead. This approach entails thinking of the second-stage design matrix **Z** as a rational basis for choosing a penalty function for penalized likelihood. Specifically, the penalty function based on (2),

$$\mathbf{P} = \tilde{\beta}_P'(\mathbf{I} - \mathbf{H})'(\mathbf{I} - \mathbf{H})\tilde{\beta}_P \quad (6)$$

could be used to compute hierarchical estimates of the coefficients $\tilde{\beta}_{\mathbf{P}}$ by penalized likelihood. This corresponds to a weighted sum-of-squared-residual penalty for departures of $\tilde{\beta}_{\mathbf{P}}$ from the linear model $\mathbf{Z}\pi$. The maximum penalized likelihood estimates are obtained by maximizing **L-P**/$2\tau^2$, where **L** is the conventional loglikelihood derived from (1). Hence, τ^2 is the inverse of the usual smoothing parameter in penalized likelihood (15).

Applications of hierarchical modeling

Hierarchical models have been used successfully in numerous investigations. In longitudinal studies, one can use hierarchical approaches to analyze repeated measurements. For example, Hui and Berger (16) used a hierarchical model to estimate bone loss in postmenopausal women. In their application, conventional estimates of decreasing bone mass from consecutive measures for each subject had a high degree of variability due to the limited data for some women. However, by applying a higher level to model the age-specific bone loss using all of the data, they obtained estimates that were generally much more reasonable. Additional technical details for using hierarchical models in longitudinal studies can be found elsewhere (17).

For case-control studies, Thomas et al. (14) used a hierarchical model to estimate 684 log odds ratios corresponding to 57 occupational exposures and 12 cancer sites, while Greenland (5) applied a slightly different model to estimate 84 log odds ratios corresponding to 7 occupational exposures and 12 cancer sites. Witte et al. (6) extended these hierarchical approaches to estimate log odds ratios for 87 dietary items and breast cancer. These applications all used conventional logistic regression as the first-stage of a hierarchical model. Thomas et al. (14) assumed independence of the resulting estimates and a common prior distribution, while Greenland (5) and Witte et al. (6) added second-stage models to incorporate information about the similarities between first-stage exposures and/or outcomes. In each application, this "borrowing of strength" by the hierarchical model shrunk extreme and unstable regression coefficient estimates toward more moderate and stable estimates, resulting in hierarchical estimates that were better than the conventional estimates. Greenland (3) and Witte and Greenland (7) present results from simulation studies comparing conventional

maximum-likelihood with hierarchical estimation of multiple logistic regression coefficients from case-control studies. Simulation results indicated that hierarchical models can offer substantial improvement over conventional models when evaluating multiple exposures, even when the second-stage model is seriously misspecified.

Cancer mapping has used hierarchical models for estimating effects according to geographic area (18). For example, Clayton and Kaldor (19) used a hierarchical model to estimate lip cancer incidence in Scottish counties. Their hierarchical approach incorporates into higher level models relevant factors (e.g., degree of urbanization), internal estimation of age effects, and allows for spatial correlation of random area effects (20). This model shrunk extreme and unstable standardized mortality ratios towards a regional average, resulting in more reasonable hierarchical estimates.

Thomas et al. (8) presented a hierarchical empirical-Bayes approach for testing associations with large numbers of candidate genes in the presence of environmental risk factors. They investigated this approach by application to human leukocyte antigen (HLA) associations in insulin-dependent diabetes mellitus (IDDM), and by a simulation study designed to reflect situations they have observed in family studies of IDDM. Their hierarchical approach assumed that the log relative risks for all alleles at a given locus are exchangeable and they modeled the covariance between two haplotypes as a function of the number of alleles they share, and the marginal strength of the effects of these alleles. Simulation results indicated that hierarchical modeling was superior to maximum likelihood. In particular, when there were no haplotype effects, empirical-Bayes estimates were closer to the true value than maximum-likelihood estimates for 75 percent of the alleles, and the empirical-Bayes estimates were more stable as well. When there were haplotype effects, empirical-Bayes was also superior because maximum likelihood models were often unable to fit without first using the data to select a subset of variables.

Hierarchical models have also seen use in experimental studies. For example, DuMouchel and Harris (21) developed a hierarchical approach that combined potency measures obtained in different species in order to conduct inter-species extrapolation. They applied this approach to the results of studies on 10 environmental hydrocarbon mixtures; intervals of posterior uncertainty that had spanned six orders of magnitude were reduced to spanning just two orders of magnitude. The fourth Advisory Committee on the Biological Effects of Ionizing Radiation (22) also applied this approach to estimate the association between high-linear energy transfer (LET) radiation (plutonium and radium) and human bone cancer risk using results from animal studies. Meng and Dempster (23) performed a hierarchical toxicological analysis of tumors occurring at 17 separate sites in rats. All of these experimental applications of hierarchical modeling provided substantial benefits over conventional analytic techniques. In addition, Louis (24) gives an overview and application of hierarchical models for improving analysis of biopharmaceutical data.

Based on the successful application of hierarchical models in a variety of situations and the theoretical and simulation work that indicates the potential improvement available when incorporating higher level models (3-5, 7), it is recommend that statisticians and epidemiologists incorporate this approach into their set of analytic tools. Specifically, I suggest presenting results from both conventional and hierarchical models. Of course, the potential improvement available with hierarchical approaches does require reasonable higher level models; but, as long as this requirement is met, hierarchical modeling will generally give better estimates than (one-stage) conventional maximum likelihood. For those interested in using this approach, some commercial software packages exist (e.g., HLM, 25); in addition, SAS code for hierarchical modeling is available at URL http://darwin.cwru.edu/~witte (26).

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Cost-Effectivenes Analysis (Continued)

Assessing the economic efficiency of an intervention or treatment procedure via the methods of CEA requires information on disease and treatment history, as well as information on costs. This information is seldom known with certainty for a number of reasons. The required data on intervention costs and consequences can rarely be obtained from a single source. Instead, data are often obtained from a mixture of sources, including empirical observations (e.g., clinical trials) and expert opinion [Gold *et al.* 1996]. Value judgments may play a part in pinpointing data values or there may be disagreement as to which methodology to employ when conducting a CEA [Drummond *et al*. 1997]. Therefore, there is an inherent element of uncertainty in the CE ratio.

In quasi-experimental designs (which are common in public health research), the accuracy of the CE ratio depends on the magnitude of error in estimating the costs and consequences of the program being evaluated. The main types of errors are associated with study particulars, such as design and data specification (including sample size and random variation within the population, for example), as well as with effect estimation errors.

One method – indeed, the most popular method historically – for addressing uncertainty in CEAs

is to conduct multiple sensitivity analysis [Briggs 1995]. In a sensitivity analysis, one or more key parameters of the cost or effectiveness model is varied, perhaps from a worst-case to best-case value, and the CE ratio is recalculated. If the CE ratio is little affected by such manipulations, so that the main conclusions of the analysis are unchanged, then the CEA is considered robust. If, on the other hand, the results of the analysis are sensitive to the particular parameters values (hence to the uncertainty in the analysis), then the main conclusions should be accepted with caution, if at all. Some of the main criticisms of the sensitivity analysis approach to uncertainty include the inherent subjectivity in selecting which parameters to vary, and the range of parameter values to be considered; the difficulty of assessing the influence of more than one parameter at a time (i.e., conducting multivariate sensitivity analyses); and ambiguity in interpreting the results of a sensitivity analysis (e.g., how much credence should be placed in the results of a worst case analysis if the worst case scenario is exceedingly unlikely ever to occur?).

Recently, attention has focused on statistical methods for quantifying the uncertainty in CEAs and, especially, developing methods to estimate confidence intervals around CE ratio point estimates. Statistical methods and sensitivity analysis may be used in conjunction with one another. Confidence intervals are useful for specifying the probable range of a particular statistic, such as a CE ratio. By definition, there is a 95% chance that the "true" value of the CE ratio lies within the range specified by the 95% confidence interval. That is, if a quasi-experiment were repeated a very large number of times, approximately 95% of these experiments would produce confidence intervals that contain the "true" value of the CE ratio.

Calculating 95% confidence intervals for costs or effects separately entails knowing the distributions, means, and variance of these parameters, as well as the overall sample size [Polsky *et al.* 1997]. Because the standard error of either costs or effects is unbiased and efficient, and because the cost and effect distributions approach normality when the respective sample sizes are sufficiently large, the confidence estimates calculated from these cost or effect estimates are said to be reliable. Nevertheless, properties such as the unknown distribution of the CE ratio, the unknown estimator of the variance of the ratio of two random variables, and the lack of an unbiased and efficient estimator of the CE ratio's standard error prevent the direct calculation of the confidence interval.

There are two main schools of thought for calculating confidence intervals: the classical versus Bayesian school of thought. The main difference between classical and Bayesian methodologies relates to the relevant information needed to estimate parameter values. The classical statistician relies on actual data to predict the "true" value/distribution/frequency of parameters. Bayesians rely on information provided by the analyst or decision maker on the likelihoods of possible parameters, prior to data collection. Once a prior distribution is specified, based upon these likelihoods, the prior distribution information is combined with the actual data set, which results in the posterior distribution, describing the likelihoods of all possible values (from prior distribution, and from data). This confidence interval is then estimated based upon the mean of the posterior distribution (Gold et al., 1996). Empirical Bayesians also rely on the information given by the analyst or decision maker on the likelihoods of possible parameters prior to data collection, but only partially. The other information for the prior distribution comes from the actual data. Once the prior distribution is specified, based upon these likelihoods, from expert opinion and actual data, the confidence interval (CI) is then estimated similarly to the Bayesian technique (Louis, 1991, Gold et al., 1996). Classical and Bayesian methods are equivalent for large sample sizes, and if the prior distribution dictates uniform values of parameters (Berger and Berry, 1988, Gold et al., 1996).

Classical methods are further broken down into parametric and non-parametric methods. The Taylor series or delta method uses the Taylor series expansion to estimate the variance of the CE ratio (assumption entails normal distribution). The Fieller theorem relaxes the assumption of normality, and the variance of the CE ratio is based upon the assumption that the numerator and denominator of the CE ratio follow a bivariate normal distribution (Chaudhary and Stearns, 1996, Gold et al., 1996, Polsky et al., 1997, Laska et al., 1997a).

For bootstrap methods, instead of estimating the variance of the CE ratio directly through use of a formula, random draws with replacement are

taken from an existing data set forming random samples (typically, 1000 draws, Efron and Tibshirani, 1993, Polsky et al., 1997). The CE ratio is calculated for each sample (bootstrap estimates), and the mean and standard deviation are calculated based on the 1000 samples created. The parametric bootstrap method assumes that the CE ratio is normally distributed. However, other types of bootstrap methods do not assume the CE ratio is normally distributed. The percentile bootstrap method entails using upper and lower percentiles of bootstrap estimates to calculate upper and lower CIs. The percentile bias corrected bootstrap method adjusts for bias through algebraic adjustments (Chaudhary and Stearns, 1996, Briggs et al., 1997), and the percentile bias corrected and accelerated bootstrap method adjusts for bias and skewness through algebraic adjustments (Briggs et al.,1997). Finally, the percentile-t method (Briggs et al., 1997) adjusts for bias in a different way from previous methods, namely, the bootstrap estimate of the CE ratio is estimated and standardized. The bootstrap process is then repeated in order to obtain an estimate of the standard error of the standardized CE ratio.

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Meet the Editors

Raymond G. Hoffmann completed his B.S. in Electrical Engineering from the University of Wisconsin in Madison. He completed the Master of Science degree in Mathematics from the Univeersity of Wisconsis, Milwaukee and received his Ph.D in Biostatistics from Johns Hopkins University . He is interested in the design of hospital-based and population-based studies. His areas of research are generalized linear models applied to clinical trials in AIDS , longitudinal studies, time series models for biomedical data, and spatial models for neuro-imaging. He is active in the use of administrative data, such as HCFA and registry data, such as SEER, for the evaluation of health services and disease epidemiology data. He was chosen as the outstanding statistician from the Milwaukee Chapter of the American Statistical Association in 1989, and has been president of the local chapter and the chapter representative to the national American Statistical Association. Dr. Hoffmann is currently Associate Professor in the Divison of Biostatistics at the Medical College of Wisconsin in Milwaukee, Wisconsin and has been the statistician at the Medical College of Wisconsin's General Clinical Research Center since 1986.

Deborah V. Dawson completed her B.A. in Mathematics and Biology at Montclair State College, (now Montclair State University) in New Jersey. She received the Master of Science degree in Biostatistics from Johns Hopkins University, and the Ph.D., also in Biostatistics, from the University of North Carolina at Chapel Hill. Dr. Dawson is currently Associate Professor in the Department of Epidemiology and Biostatistics in the School of Medicine at Case Western Reserve University, Cleveland, Ohio. Her methodological work is concerned with the development of statistical methods for the study of human genetic diseases, especially those related to disorders characterized by delayed age of onset and problems of ascertainment bias. Other research interests include the genetic epidemiology of

autoimmune, developmental and behavioral disorders, the genetics of the immune response, and population genetic models, including applications in the areas of transplantation, transfusion, vaccine production, and reproductive biology.

ACTIVITIES in BALTIMORE

Short Courses:

The analysis of correlated data with application to epidemiologic research (David Kleinbaum, Emory University). Saturday (all day).

Statistical Searches for Disease Genes (Bruce Weir, NCSU). Tuesday (all day).

Invited Sessions:

Methods for handling missing data, measurement error, and outliers in longitudinal epidemiological data:

Modern computational methods for conditional inference concerning discrete regression models:

Assessing individual causality from aggregate data:

Special Contributed Sessions:

Future direction of longitudinal data analyses:

Covariate measurement error in failure-time regression models:

Use of propensity-score methods in pharmaco-epidemiologic studies:

Regular Contributed Sessions:

Survival methods: truncation, censoring and overrunning:

Risk factors for growth, aging and death: Gender related health issues: Wednesday

Diagnostic tests: ROC curves, imperfect "gold" standards and sequential tests:

Contributed Poster Sessions

A Comparison of Sexual Activity Models for AIDS Prevention

For the fifth year we will publish Proceedings. This year we are publishing jointly with the Section on Health Policy Statistics.

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