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Estimation of Cumulative Odds Ratios

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PURPOSE: Standard estimation of ordered odds ratios requires the constraint that the etiologic effects of exposure are homogenous across thresholds of the ordered response. We present a method to relax this often-unrealistic constraint.
METHODS: The kernel of the proposed method is the expansion of observed data into "person-thresholds." Using standard statistical software, for each subject we create a separate record for each response threshold and then apply binary logistic regression to estimate generalized cumulative odds ratios for one or more exposures.
RESULTS: Two examples demonstrate that the proposed method provides increased flexibility in assessing the etiologic effects of exposures. A Monte Carlo simulation study supports the proposed approach by suggesting the estimated cumulative odds ratios are unbiased with proper confidence interval coverage attained by use of generalized estimating equations.
CONCLUSION: The proposed method provides simple estimates of ordered odds ratios that allow the etiologic effects of exposure to vary across levels of the ordered response.
Ann Epidemiol 2004;14:172–178.

KEY WORDS: Ordered Response, Cumulative Logit Model, Epidemiologic Methods, Odds Ratio.

INTRODUCTION

Epidemiologists frequently encounter ordered responses, but rarely present results of analyses using models for ordered responses. Many standard ordered response logit models, such as the cumulative logit (i.e., proportional odds), continuation-ratio, and adjacent-category logit models (1–3) constrain the treatment or exposure X to have equivalent effects on transitioning among thresholds of an ordered response Y. This constraint translates into the threshold-specific log odds ratios being held equal. Several authors have underscored the need to assess the assumption of homogeneity of threshold-specific effects in such models, which provide a single effect estimate averaged over thresholds (4–11). We previously reported a method to relax this homogeneity assumption for the ordered odds ratio obtained by the continuation-ratio model (9). Herein, we use two empirical examples to demonstrate a different but related method also using standard statistical software to estimate ordered odds ratios from the cumulative logit model, which relaxes the assumption of homogenous threshold-specific effects. In addition, we evaluate some of the statistical properties of the proposed method by Monte Carlo simulation.

METHODS

Cumulative Logit Models

Consider an ordered response Y, and a vector of covariates **x**, collected on *N* independent subjects. To such data, one may fit a cumulative logit model of the form

$$\log\left[\frac{\Pr(Y \geq y_j \mid \mathbf{x})}{\Pr(Y < y_j \mid \mathbf{x})}\right] = \alpha_j + \mathbf{x}'\beta, \quad j = 1,2,\ldots,k-1, \text{model } 1$$

where the y_j are the cut-points for Y, the α_j represent baseline logits of conditional response probabilities, and β are the log odds ratios relating components of **x** to the ordered response Y. Note that β in model 1 does not depend on *j*, the point at which Y is dichotomized. To clarify, if Y has *k* levels, then $k-1$ logits are formed. For example, a 4-level ordered response, Y = {0,1,2,3}, would have 3 logit comparisons. With a cumulative logit model, the three specific logit comparisons are $Y \geq 1$ vs. $Y < 1$, $Y \geq 2$ vs. $Y < 2$, and $Y \geq 3$ vs. $Y < 3$. The estimated log cumulative odds ratio, $\hat{\beta}$, can be thought of as a weighted average of the $k-1$ threshold-specific log odds ratios. Model 1 is usually estimated by maximum likelihood. For example, when the SAS

Dr. Cole was partly supported by the National Institute of Allergy and Infectious Diseases by means of the data coordinating centers for the Multicenter AIDS Cohort (U01-AI-35043) and Women's Interagency HIV studies (U01-AI-42590). Dr. Ananth was partly supported by the National Institute of Child Health and Human Development (R01-HD-38902).

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Received November 18, 2002; accepted August 18, 2003.

1047-2797/04/$–see front matter
doi:10.1016/j.annepidem.2003.08.003

program LOGISTIC is fit with a response variable that has greater than 2 levels, model 1 is automatically implemented with the parameter estimates obtained via maximum likelihood.

A fully generalized cumulative logit model, which relaxes the cumulative odds assumption, can be formulated as

$$\log\left[\frac{\Pr(Y \geq y_j \mid \mathbf{x})}{\Pr(Y < y_j \mid \mathbf{x})}\right] = \alpha_j + \mathbf{x}'\beta_j,\ j = 1,2,\ldots,k-1, \text{model } 2$$

where the β_j are the threshold-specific log odds ratios. The cumulative logit model (model 1) is nested within the fully generalized cumulative logit model (model 2). There are several other (nested) models that fall between the cumulative and fully generalized cumulative logit models described above, which were termed partial proportional odds models by Peterson and Harrell (10). For example, a subset of the $k-1$ threshold-specific log odds ratios may be constrained to be equal, while the complement of the subset is left unconstrained. Alternatively, the $k-1$ threshold-specific log odds ratios may be modeled as an increasing or decreasing linear or curvilinear function. Additionally, one may constrain a subset of the vector of covariates **x** to have cumulative odds, while specifying the complement of the subset to be unconstrained or partially constrained.

Person-threshold Data

The method we espouse is accomplished by expanding the data in a fashion parallel to discrete person-time logit models for survival analysis (12,13). We previously described (9) a well-known variant of this data expansion approach (4) using the data from example 1 for an alternative formulation of ordered logistic regression, namely, the continuation-ratio model. To expand the observed data to a person-threshold format for the generalized cumulative logit model, each subject receives a number of records equal to the number of response thresholds. All covariates remain threshold-constant (e.g., parallel to time-constant variables in survival-time data) except for a threshold variable that marks which of $k-1$ thresholds the record corresponds to and an indicator variable, D_j, which is set to one if the threshold was reached and zero otherwise. The generalized cumulative logit model is fit to the person-threshold data by

$$\text{logit } \Pr(D_j = 1 \mid \mathbf{x}) = \alpha_j + \mathbf{x}'\beta_j, \quad j = 1,2,\ldots,k-1, \text{model } 3$$

where the set of intercepts α_j are equal to the coefficients for the indicators of the $k-1$ specific thresholds. A similar implementation was described by Stokes et al (21). Note that the expanded data set will have a number of records equal to the product of the number of subjects and thresholds. This person-threshold data formulation explicitly weights the subjects' contributions as is necessary to recover a cumulative odds ratio. Using the person-threshold data, a standard binary logistic regression model may then be fit to derive estimates of the cumulative or generalized cumulative odds ratios from models 1 or 2, depending on specification. For instance, regressing the threshold indicator variable on exposure X and including $k-1$ indicator variables for the $k-1$ thresholds fits a cumulative logit model (model 1). However, including exposure-by-threshold interactions, between each of the $k-1$ threshold indicators and the covariate of interest X, fits a fully generalized cumulative logit model (model 2), which separately quantifies the effect of the covariate on *each* threshold. These interaction effects are analogous to exposure-by-time interactions in pooled logistic regression, which can be used to test the assumption of proportional hazards.

Modification to these interactions allows a general method for relaxing constraints for the X effect over thresholds, and thereby allowing the fit of partially generalized cumulative logit models. For example, including threshold-specific interactions for a subset of the thresholds produces non-cumulative odds ratios for those thresholds and a single cumulative odds ratio for the complement of the subset. A further modification can be gained by creating a threshold-specific variable (δ) that is the product of the exposure and the threshold number minus one (j-1). Including this variable in addition to the exposure X allows a linear constraint on the threshold-specific odds ratios beyond the first threshold (10). This idea generalizes to curvilinear effects as well (14). Partially generalized cumulative logit models which allow a subset of the vector of covariates **x** to have cumulative odds and the balance of the subset to have non-cumulative odds may be fit by including the covariate-by-threshold interaction terms for the balance of the subset of covariates.

In the creation of the person-threshold data, we inadvertently induce a within-person dependence structure since $k-1$ observations are created for each observed subject. This dependence does not cause any problems when fitting a fully generalized cumulative logit model (model 3). This can be seen from the fact that the fully generalized model consists of $k-1$ equations, each with a completely distinct set of parameters. Maximum likelihood estimation of the entire set is equivalent to separately estimating each equation using a single observation from each person. However, problems arise when fitting any model that constrains the threshold-specific effects for any covariate using person-threshold data (i.e., cumulative or partially generalized cumulative logit models). Therefore, we used generalized estimating equations (15) with an autoregressive working covariance matrix to account for the incurred dependence. We chose an autoregressive covariance matrix because such a specification assumes that each threshold is correlated with the prior adjacent threshold, as might be expected with

an ordered response. Choosing either an exchangeable or unstructured working covariance matrix did not appreciably change the results of the data examples or the simulations. Alternatively, one could use a bootstrap resampling approach (16).

Because the cumulative logit model is nested within the generalized cumulative logit model, generalized score statistics (for the generalized estimating equations) provide a method to assess the validity of the assumption that the threshold-specific odds ratios are equal. Under the null hypothesis that the threshold-specific odds ratios are equal, the generalized score statistic is distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters between the nested models.

Example 1: Degree Of Perinatal Laceration

In Table 1, we provide data presented by Ananth and Kleinbaum (5) and Cole and Ananth (9). These data reflect the degree of perinatal laceration (none, 1°, 2°, 3°, and 4°), a 5-level ordered response, in relation to a midline episiotomy (further details about these data are available in reference (5)). The expanded data for three hypothetical subjects from Table 1 is shown in Table 2.

The cumulative odds ratio obtained by maximum likelihood is 3.0 [95% confidence interval (CI), 2.5, 3.7]. As can be seen in Table 3, the person-threshold cumulative odds ratio is 3.5 (95% CI, 2.8, 4.3). The assumption of equal slopes does not appear justified as the non-cumulative odds ratios are 2.9, 4.4, 5.9, and 7.5, and the generalized score statistic for homogeneity of slopes is large ($\chi^2 = 95$ on 3 degrees of freedom, $p < 0.001$). Although inference is unchanged, this generalized score statistic based on the estimating equations is smaller than the likelihood ratio score statistic for homogeneity of slopes from the maximum likelihood model ($\chi^2 = 219$ on 3 degrees of freedom, $p < 0.001$). These results indicate that the effect of episiotomy is stronger at higher levels of perinatal laceration. In Figure 1, panel A depicts the parallel effects for episiotomy (on the cumulative logit) from the cumulative model, while panel B shows the non-cumulative effects from the generalized cumulative logit model.

If we wished to constrain the effect of the last threshold and estimate its effect combined with the second to last threshold due to the small numbers at the more extreme levels of the response variable, then we may wish to fit a partially generalized cumulative logit model. These results are also shown in Table 3. Here, the collapsed model appears compatible with the data, as the incremental increase in fit by separately estimating the last two threshold-specific odds ratios is small (generalized score $\chi^2 = 1.5$ on 1 degree of freedom, $p = 0.220$). Further, one may, based on prior knowledge or by examining the threshold-specific effects in Figure 1 (panel B), want to explore a linear increase in the log odds ratios across thresholds using another partially generalized cumulative logit model. In this example, under a log-linear constraint, the estimated odds ratios for the four thresholds are 3.0, 4.2, 5.9, and 8.4. Note that these log-linearly constrained odds ratios closely mirror the fully generalized cumulative odds ratios shown in Table 3. This partial (log-linear) generalized cumulative logit model appears to be an improvement on the standard cumulative logit model, as evidenced by the non-zero estimate of δ (95% CI, 0.3, 0.4).

TABLE 1. Joint frequency distribution of episiotomy and perinatal lacerations among 10,964 women*

	Degree of perinatal laceration				
Episiotomy	0	1	2	3	4
None	9,238	140	71	131	37
Midline	1,204	8	8	89	38

*Data from Ananth and Kleinbaum (5)

TABLE 2. Person-threshold data expanded for 3 hypothetical subjects from Table 1*

ID	Midline episiotomy	Degree of laceration	Threshold	Reached
1	0	0	1	0
1	0	0	2	0
1	0	0	3	0
1	0	0	4	0
2	0	3	1	1
2	0	3	2	1
2	0	3	3	1
2	0	3	4	0
3	1	4	1	1
3	1	4	2	1
3	1	4	3	1
3	1	4	4	1

*ID = 1 corresponds to a subject with data (from Table 1) episiotomy = 0 (none) and degree (of laceration) = 0; ID = 2 a subject with data episiotomy = 0 and degree = 3; ID = 3 a subject with data episiotomy = 1 and degree = 4.

Example 2: Retinopathy Status

In Table 4, we provide a summary of data previously analyzed by Bender and Grouven (8). These data capture the 6-year follow up retinopathy status (none, nonproliferative, and advanced), a 3-level ordered response, in relation to baseline smoking status (Yes/No) for 613 type I diabetic patients. For further details about these data please see reference (17). Following the description given above for the creation of the person-threshold data set, we have 1226 records for the 613 subjects. As Bender and Grouven (8), we adjusted for duration of diabetes, diastolic blood pressure, and glycosylated hemoglobin, each with a single linear term. The mean duration of diabetes was 15 (SD = 7) years. The mean diastolic blood pressure was 80 (SD = 7) mmHg. The mean glycosylated hemoglobin was 7.8 (SD = 1.3) percent.

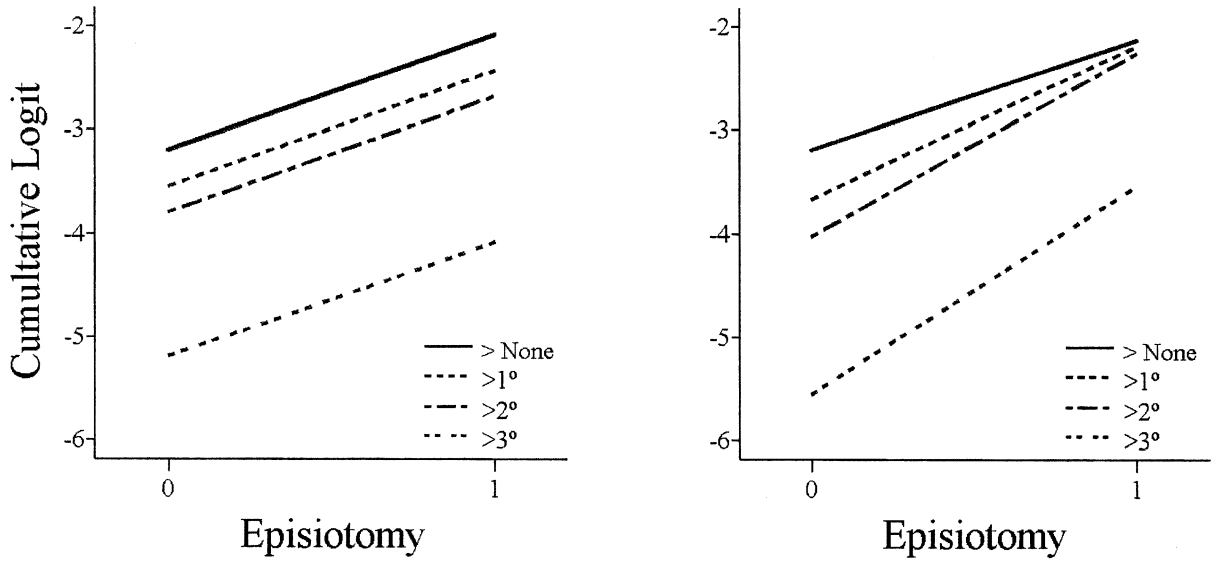

FIGURE 1. Panel A depicts the cumulative logit for those with and without episiotomy for each ordered response threshold for the cumulative odds model, while panel B depicts the cumulative logit for the generalized cumulative odds model.

The cumulative odds ratio obtained by maximum likelihood is 1.3 (95% CI, 0.9, 1.9). As can be seen in Table 5, the person-threshold cumulative odds ratio is also 1.3 (95% CI, 0.9, 1.9). This summary of the threshold-specific odds ratios commingles two effects on opposite sides of unity as the first threshold odds ratio is 1.6 and the second is 0.9. The odds ratio of 1.6 indicates that the odds of nonproliferative or advanced disease (vs. no disease) are 60% higher among smokers compared with nonsmokers. While the odds ratio of 0.9 indicates that the odds of advanced disease (vs. none or nonproliferative disease) are not increased and possibly slightly lower among smokers compared with nonsmokers. Once again, the assumption of equal slopes (i.e., βs) does not appear justified. The generalized score statistic testing the equality of slopes for smoking status yields a χ^2 of 6.38 on 1 degree of freedom ($p = 0.012$), confirming the intuition gained from regarding Figures 2A and 2B, which depict the changing sign of slopes for the cumulative and generalized cumulative logits by baseline smoking status (in unadjusted retinopathy data).

TABLE 3. Ordered regression models for perinatal laceration data

Model		Odds ratio	95% CI
Non-cumulative	$e^{\beta 1}$	2.90	2.37,3.54
	$e^{\beta 2}$	4.37	3.51,5.44
	$e^{\beta 3}$	5.86	4.61,7.43
	$e^{\beta 4}$	7.52	4.76,11.9
Partial cumulative	$e^{\beta 1}$	2.83	2.31,3.48
	$e^{\beta 2}$	4.23	3.37,5.30
	$e^{\beta 34}$	5.57	4.32,7.17
Partial (log-linear)	e^{β}	2.95	2.39,3.63
cumulative	δ	0.35	0.28,0.42
Cumulative	e^{β}	3.48	2.82,4.30

Monte Carlo Simulations

To examine this method of fitting cumulative and generalized cumulative logit models, we performed a Monte Carlo simulation study. We generated independent observations of data $O = (X, Y)$, where X was a random Bernoulli variable with probability .5 and Y was a random 4-level ordinal response dependent on X through the generalized cumulative logit model (model 2). We set $\hat{\beta}$ so that the distribution of Y under the null was 40%, 30%, 20%, and 10% for $Y = 0$, 1, 2 and 3, respectively. We report three sets of results, with the threshold-specific log odds ratios set at $\beta_j = \{0,0,0\}$, $\beta_j = \{1,.5,0\}$, and $\beta_j = \{1,1,1\}$. Using model 2, with α_j and β_j set as described above, we calculated the cumulative distribution function for Y, which translates into a step function based on three probabilities, namely

TABLE 4. Joint frequency distribution of smoking and retinopathy status at follow up for 613 diabetic individuals*

		Retinopathy status at follow up	
Smoking	None	Nonproliferative	Advanced
No	191	42	55
Yes	197	76	52

*Data from Bender and Grouven (8).

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TABLE 5. Ordered regression models for retinopathy status data

Model*		Odds ratio	95% CI
Non-cumulative	$e^{\beta 1}$	1.57	1.03,2.38
	$e^{\beta 2}$	0.90	0.58,1.41
Cumulative	e^{β}	1.28	0.88,1.88

*Adjusting for diabetes duration, diastolic blood pressure, and glycosylated hemoglobin.

$\Pr(Y \geq y_i | X = x)$, where $j = 1, 2, 3$. We then generated a uniform random variable and compared it to the inverse distribution function to determine Y. We present the average (of 2000 samples) point estimate and standard error for the cumulative logit model fit by maximum likelihood and both the cumulative and generalized cumulative logit models fit by generalized estimating equations on the person-threshold data. In addition, we provide the estimated coverage probabilities for the two-sided 95% confidence interval and the standard deviation of the 2000 point estimates as a Monte Carlo simulation estimate of the standard error. A single summary odds ratio from a cumulative odds model has no hope of recovering a set of true heterogeneous threshold-specific odds ratios. Therefore, for the scenario where the cumulative logit model is mis-specified because of heterogeneous threshold-specific odds ratios, namely when $\beta_j = \{1,.5,0\}$, percent confidence interval coverage is calculated with respect to the parameter that minimizes the Kullback-Leibler information criterion (18,19), which is an information-weighted mean of the threshold-specific odds ratios and is determined by fitting of the maximum likelihood cumulative odds model to the expected table of counts.

The proposed method, using a person-threshold data set, appeared unbiased (on average, the method recovered the correct point estimate, Table 6) and compared well to the maximum likelihood estimates. The average of the estimated standard errors was nearly equal to the observed standard deviation of the estimates across 2000 samples. Coverage of the 95% confidence intervals was close to nominal. As expected, the models that incorrectly specified homogenous threshold-specific effects of X recovered a weighted average of the threshold-specific log odds ratios.

DISCUSSION

This proposed method for fitting generalized cumulative odds models improves upon the standard methods for fitting the cumulative logit model by allowing for greater flexibility in fitting the effects of covariates, while requiring only a binary logistic regression model with indicators for thresholds and generalized estimating equations. Such binary logistic regression models, with the estimation of parameters based on generalized estimating equations, are common to most major statistical software packages. The person-threshold formulation easily generalizes to include multiple covariates to account for confounding and interactions among covariates to assess effect measure modification. The formulation of the person-threshold data set can be easily programmed using standard statistical software packages with data management capabilities, such as SAS.

Modification of the exposure-by-threshold interactions allows a general method for relaxing constraints for the X

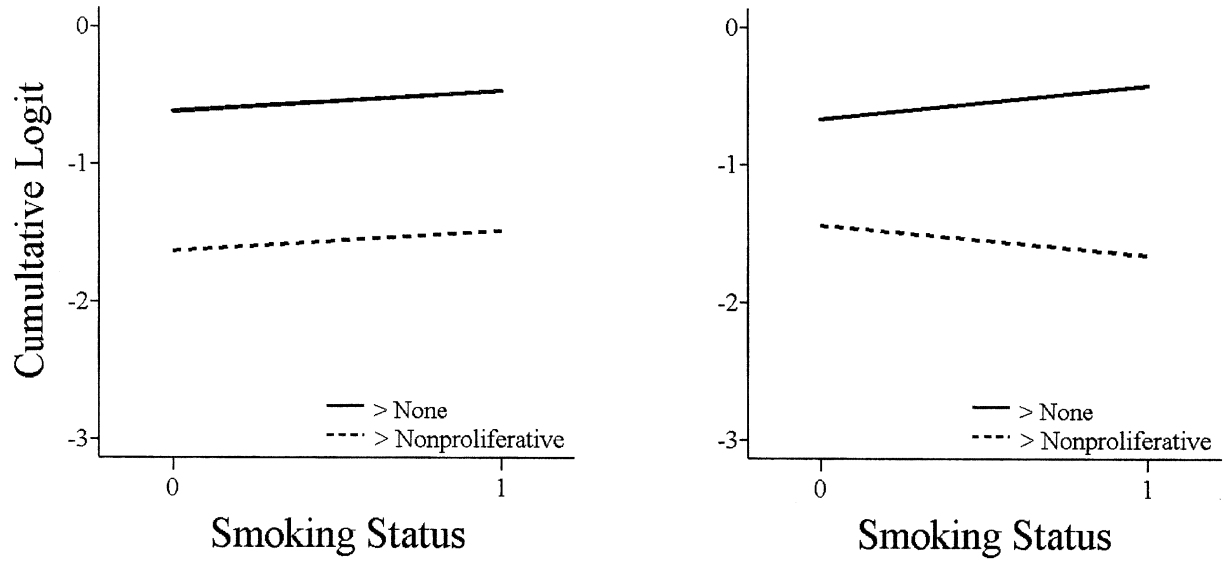

FIGURE 2. Panel A depicts the cumulative logit for smokers and non-smokers for each ordered response threshold for the cumulative odds model, while panel B depicts the cumulative logit for the generalized cumulative odds model.

TABLE 6. Monte Carlo simulation of generalized cumulative logit models based on 2000 samples of size 500

True β_j (KLIC)*	Method†	Model‡		Mean $\hat{\beta}$	Mean SE $\hat{\beta}$	SD $\hat{\beta}$¶	95% CI coverage**
0,0,0	ML	1	$\hat{\beta}_1 = \hat{\beta}_2 = \hat{\beta}_3$	−0.01	0.16	0.16	0.95
(0)	EE	1		−0.01	0.16	0.16	0.95
		2	$\hat{\beta}_1$	−0.01	0.18	0.18	0.95
			$\hat{\delta}$	0.00	0.14	0.15	0.95
		3	$\hat{\beta}_1$	−0.01	0.18	0.18	0.95
			$\hat{\beta}_2$	0.00	0.20	0.19	0.96
			$\hat{\beta}_3$	0.00	0.30	0.31	0.96
1, .5, 0	ML	1	$\hat{\beta}_1 = \hat{\beta}_2 = \hat{\beta}_3$	0.66	0.17	0.16	0.95
(0.67)	EE	1		0.67	0.17	0.16	0.95
		2	$\hat{\beta}_1$	1.00	0.20	0.19	0.96
			$\hat{\delta}$	−0.50	0.16	0.16	0.95
		3	$\hat{\beta}_1$	1.00	0.21	0.20	0.96
			$\hat{\beta}_2$	0.50	0.19	0.18	0.96
			$\hat{\beta}_3$	0.00	0.30	0.31	0.96
1,1,1	ML	1	$\hat{\beta}_1 = \hat{\beta}_2 = \hat{\beta}_3$	1.00	0.17	0.16	0.96
(1)	EE	1		1.00	0.17	0.16	0.96
		2	$\hat{\beta}_1$	1.00	0.20	0.19	0.96
			$\hat{\delta}$	0.00	0.14	0.14	0.95
		3	$\hat{\beta}_1$	1.00	0.21	0.20	0.96
			$\hat{\beta}_2$	1.00	0.19	0.18	0.96
			$\hat{\beta}_3$	1.01	0.26	0.27	0.95

*Kullback-Leibler information criterion, assuming: $\hat{\beta}_1 = \hat{\beta}_2 = \hat{\beta}_3$.
†Maximum likelihood, estimating equation.
‡Model 1 assumes cumulative, model 2 a log-linear change, and model 3 non-cumulative odds.
¶Standard deviation of 2000 point estimates.
**Confidence interval (CI) coverage is the proportion of 2000 95% CIs that include the true value.

effect over thresholds as illustrated by Petersen and Harrell (10) and Scharfstein and colleagues (14). We emphasize caution regarding the exploration of numerous partially constrained models. When such searches are conducted arbitrarily they capitalize on chance. Therefore, specification of particular partially constrained models should be either stated in a prior research protocol or put to sensitivity analysis [e.g., bootstrapping the entire model selection process (20)]. Also, note that the present models are based on estimating equations and are therefore not equivalent to a likelihood-based approach. Although we did not observe any meaningful difference in efficiency, as measured by the difference in the empirical standard deviations for the maximum likelihood and estimating equation methods in the simulations, a likelihood-based approach will be maximally efficient if the model is correct. Any gain in efficiency by use of a maximum likelihood method would be at the cost of requiring the analyst to program the likelihood explicitly in a general maximization routine, such as the SAS program NLMIXED.

Compared with a cumulative logit model, generalized cumulative logit models will commonly have less efficiency (due to the increased number of parameters) but likely will represent the threshold-specific exposure effects better when these effects are heterogeneous. This is a straightforward example of the ubiquitous tradeoff between bias and efficiency in statistics. There are alternative formulations to an ordered response model that may better suit a specific application, such as the continuation-ratio model (which compares levels 2+ vs. 1, levels 3+ vs. 2, level 4 vs. 3, etc.) and the adjacent-category logit model (which compares level 2 vs. level 1, 3 vs. 2, 4 vs. 3, etc.). Greenland gives some biologic considerations that can be used to make initial choices among the formulations (2).

In summary, the proposed alternative method for fitting cumulative and generalized cumulative odds ratios allows great flexibility over the assumption of homogeneity of threshold-specific covariate effects, and may allow more appropriate application of models for ordered responses than standard methods. The proposed method will be of great benefit to epidemiologists who frequently encounter studies with ordinal responses.

We thank Professor Sander Greenland for helpful suggestions and Dr. Ralf Bender for the retinopathy data.

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