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Comparison of methods for ordinal lens opacity data from atomic-bomb survivors: univariate worse-eye method and bivariate GEE method using global odds ratio

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Abstract In analyses of bivariate ordered polytomous cataract data from atomic-bomb survivors, we compared two methods, the univariate worse-eye method, and the bivariate generalized estimating equations (GEE's) method using global odds ratio by Williamson et al. (*Journal of the American Statistical Association*, *90*, 1432–1437, 1995). When the association was large and only subject level covariates were used, model selection in the univariate and bivariate methods resulted in the same mean model and similar risk estimates. We showed that the mean parameter and the standard error (SE) in the univariate model are emphasized relative to those in the bivariate model, the biases of which are negligible when the association between both eyes is large. Large sample simulation studies indicated that the univariate Wald statistics are slightly conservative. The simulations also showed that, in bivariate cases, irrespective of the degree of association, the independence estimating equations method with robust SE, and the GEE method with model-based and robust SE are almost fully efficient in parameter estimation when only subject level covariates are included in the mean.

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1 Introduction

It is known that atomic-bomb radiation causes cataract (Choshi et al., 1983; Minamoto et al., 2004). The most recent cataract prevalence study by Minamoto et al. (2004) used the Lens Opacity Classification System II (LOCS II) (Chylack et al., 1989) in grading four major lens changes: nuclear color (NC), nuclear opacity (NO), cortical cataract (CC) and posterior sub-capsular opacity (PS). The system shows good inter- and intra-observer reproducibility (Chylack et al., 1989), which suggests that the response measurement error is small. We did not use LOCS III (Chylack et al., 1993), because the grading of cataract in LOCS III is so precise that observer bias could be relatively large, i.e., large response measurement error. The outcome variables for these lens changes in LOCS II are qualitative, ordered and polytomous. For analysis of this data, Minamoto et al. (2004) used the univariate worse-eye method—that is, the outcome of a subject is the outcome of the worst grade among the grades of both eyes—and found significant radiation dose responses in CC and PS. The worse-eye method is more conventionally used since bivariate analysis is often difficult. If we want to have estimates specific to each eye of the subject for lens opacity and to obtain a smaller standard error for the estimates, however, bivariate analysis would be most appropriate.

In ophthalmology studies, we often observe bivariate ordered polytomous data, a pair of polytomous outcomes of interest from the right and left eyes of a subject. Covariates are obtained from an individual (subject level covariate) or obtained separately from each eye of a subject (within subject level covariate). We are usually interested in the effects of such covariates on the ordered polytomous marginal probabilities and the degree of association between right and left eyes affected by the covariates.

Dale (1986) and Molenberghs and Lesaffre (1994) considered the maximum likelihood (ML) method for correlated bivariate and multivariate discrete data, respectively, using a global odds ratio association model (Plackett, 1965; Dale, 1984). Kim (1995) proposed a bivariate ML method that used polychoric correlation as a measure of association and that is an extension of the probit model for univariate dichotomous data. However, the ML method does not provide consistent estimates of parameters unless correct specifications of both the mean and association models are available. The method is also computationally inconvenient. Conversely, because of its computational convenience and the fact that it provides consistent estimates with only correct specification of the mean model, the generalized estimating equations (GEE's) approach is appropriate for analysis of multivariate correlated data although the estimation efficiency is lowered.

Liang and Zeger (1986) developed the GEE method for multivariate correlated binary data using correlation as a measure of association and showed that

the GEE estimation is highly efficient with a large sample. Sharples and Breslow (1992) conducted GEE simulations on clustered binary data with a small sample ($\leq$100) and mild non-negative correlation ($\leq$0.3) and concluded that the GEE with independence working correlation often works well. Under conditions similar to those employed by Sharples and Breslow (1992), Gunsolley et al. (1995) showed that Type I error rates in hypothesis testing with GEE were inappropriate. Miller et al. (1993) extended the GEE method to multivariate correlated ordered polytomous data. Using the method by Miller et al. (1993), Gange et al. (1995) considered the GEE method for ophthalmic application and compared the univariate method and the bivariate GEE method. Lipsitz et al. (1991) and Liang et al. (1992) developed a GEE method of analysis of clustered binary data using odds ratio as a measure of association. Using global odds ratio, an extension of odds ratio, Williamson et al. (1995) extended the method by Lipsitz et al. (1991) to bivariate ordered polytomous data. The method developed by Williamson et al. (1995) is a GEE version of the ML method by Dale (1986). Lumley (1996) and O'Hara Hines (1997) suggested that, in the analysis of clustered polytomous data, careful modeling of the working association is unnecessary and that, even if we assume a complicated working association, the estimation efficiency of the mean parameter is not gained. However, this does not necessarily indicate that the GEE estimation is fully efficient.

In multivariate analysis, in addition to the mean modeling, we need to consider associations among responses. For bivariate cases, the correlation, global odds ratio (Dale, 1984) and dependence ratio (Ekholm et al., 1995) can be considered measures of association between the responses. The correlation is the most general measure of association for any bivariate response, including continuous response and ordered or nominal discrete response. However, the correlation is most appropriate for quantitative responses. The global odds ratio provides simple interpretation and is appropriate when both responses are discrete, qualitative, and ordered (Dale, 1986, 1984). In fact, the global odds ratio does not change but the correlation changes when, for example, the three category response is scored as $\{1, 2, 3\}$ or as $\{1, 2, 4\}$. If the response category number is two, however, the correlation is also an invariant of the scoring system. The dependence ratio has a simple interpretation and a natural generalization to higher order association (Ekholm et al., 1995, 2003). Thus, since the outcome of the lens opacity is qualitative, ordered, and polytomous, the use of global odds ratio in bivariate analysis would be appropriate.

In Sect. 2, we provide the atomic-bomb posterior sub-capsular lens opacity data used in the analysis. In Sect. 3, we describe four methods of analysis: bivariate GEE by Williamson et al. (1995), the independence estimating equations (IEE's), the ML method using the global odds ratio by Dale (1986), and the (conventional) univariate worse-eye method. In Sect. 4, we apply the methods to the atomic-bomb lens opacity data. In Sect. 5, we show the difference of the parameters between the univariate and bivariate methods. A bias calculation of univariate dose response parameter relative to bivariate dose response parameter was made in a binary case. In Sect. 6, the efficiency consideration will be

given by simulation. In Sect. 7, the discussion section, some concluding remarks are made.

2 Data

An ophthalmologic prevalence study (Minamoto et al., 2004) was performed from June 2000 to September 2002 in both Hiroshima and Nagasaki at the Radiation Effects Research Foundation (RERF). The study cohort of this research comprised two groups: young subjects with age at exposure 13 years or younger and subjects who were participants of a previous ophthalmologic study (1978–1980) by Choshi et al. (1983) in the RERF Adult Health Study (AHS) cohort (Yokoro, 1991). Examinees were given explanation of the procedures and possible adverse effects of the topical mydriatic (0.5% tropicamide and 0.5% phenylephrine hydrochloride) that would be administered. The ocular lenses of the participants were examined and photographed by a physician. Original diagnoses were made by three ophthalmologists from Hiroshima University and two from Nagasaki University in their respective cities (Minamoto et al., 2004). The digital photographs were stored in a database, and a single ophthalmologist (A.M.) reviewed all the cataract diagnoses using LOCS II (Chylack et al. 1989) by scrutinizing the photographs. Each subject had a dosimetry system 2002 (DS02)-based (Young and Bennett, 2006) ocular radiation dose (Sv) with relative biological effectiveness (RBE) of 10, that is, the DS02 ocular gamma radiation dose (Gy) plus ten times the DS02 ocular neutron radiation dose (Gy) truncated at 4 Gy.

Total number of subjects who participated in this study was 877. We excluded 4 dose unknown subjects and 143 in utero exposed subjects. The number of subjects valid for analysis was 730. Since the review was made using only photographs, there were several indeterminate cases. Twenty-eight subjects were reviewed in only one eye, and 39 subjects were not reviewed in both eyes. Reviews of PS in both eyes were successfully made for 663 subjects. Table 1 shows the distribution of bivariate PS complete outcomes according to LOCS II grade. Grade PS = I expresses normal eye or no opacity, and the higher

Table 1 Distribution of PS complete outcomes in LOCSII grade

	Right eye					
Left eye	I	II	III	IV	V	Total
I	459	21	3	1	0	484
II	37	98	10	1	0	146
III	6	9	12	0	0	27
IV	0	1	2	0	0	3
V	0	1	1	0	1	3
Total	502	130	28	2	1	663

Signed-rank test for right = left: two-sided $p = 0.021$; correlation $r = 0.70$

the grade the more severe the opacity. Target outcome PS has five grades in LOCSII and the outcomes from the right and left eyes are positively correlated (Spearman rank correlation = 0.74).

3 Statistical methods

Assume that there are N people in an ophthalmology study with data for both eyes. Let X_{it} be a covariate vector, and PS_{it} denote the $K = 5$ level ordered response of PS in LOCS II for eye $t(t = 1$ for left and $t = 2$ for right) of subject i, i.e., $PS_{it} \in \{1, \ldots, 5\}$. We define random variables $Y_{itj} = I(PS_{it} = j)$, where $I(.)$ is indicator variable, $j = 1, \ldots, K$. Note that $PS_{it} = \sum_{j=1}^{K} jY_{itj}$.

3.1 Mean and global odds ratio association models

Let $\gamma_{itj} = \Pr(PS_{it} \leq j)$ be the marginal cumulative probability and define $\pi_{itj} = \Pr(PS_{it} = j)$. We then have $E(Y_{itj}) = \pi_{itj} = \gamma_{itj} - \gamma_{itj-1}$ for $j = 1, \ldots, K$ with $\gamma_{it0} = 0.0$ and $\gamma_{itK} = 1.0$. To model the marginal $\gamma_{itj} = \Pr(PS_{it} \leq j \,|X_{it})$, we use proportional odds model (McCullagh and Nelder, 1989),

$$\text{logit}(\gamma_{itj}) = \log\left(\frac{\gamma_{itj}}{1 - \gamma_{itj}}\right) = \theta_j - X_{it}^T \beta_1, \tag{1}$$

where $\theta_j, j = 1, \ldots, K-1$ are the cutoff point parameters, X_{it} is a covariate vector including subject level and/or within subject level covariates, and β_1 is a regression parameter vector. The link of the model (1) is a logistic link, and we can consider the other links to be probit or complementary log–log links. However, the proportional odds model, or logistic link for cumulative probability, is very commonly used in risk estimation for ordinal categorical data, since evaluation of odds ratio for risk variables is possible. In model (1), we assume common cutoff points for left and right eye responses. If there is a difference in cutoff points between the left and right responses, we can include "side" within subject level variable in the covariates, which is defined as the common difference between cutoff points of left and right eye responses. When only subject level covariates are used in the mean, the marginal response probabilities of left and right eyes are symmetric.

Let $F_{ijj'} = \Pr(PS_{i1} \leq j, PS_{i2} \leq j')$ be the joint cumulative probability for $j, j' = 1, \ldots, K$ of subject i. Note that $F_{ijK} = \gamma_{i1j}$ and $F_{iKj'} = \gamma_{i2j'}$. We define the global odds ratio association, GOR, (Dale, 1984) as,

$$\begin{aligned}\psi_{ijj'} &= \frac{\Pr\left(PS_{i1} \leq j, PS_{i2} \leq j'\right) \cdot \Pr\left(PS_{i1} > j, PS_{i2} > j'\right)}{\Pr\left(PS_{i1} > j, PS_{i2} \leq j'\right) \cdot \Pr\left(PS_{i1} \leq j, PS_{i2} > j'\right)} \\ &= \frac{F_{ijj'}\left(1 - \gamma_{i1j} - \gamma_{i2j'} + F_{ijj'}\right)}{\left(\gamma_{i2j'} - F_{ijj'}\right)\left(\gamma_{i1j} - F_{ijj'}\right)},\end{aligned} \tag{2}$$

where, for binary case, the global odds ratio amounts to an odds ratio for binary outcomes between left and right eyes. To describe the dependence of the association on covariates, one can model the global odds ratio in log linear form (Dale, 1986, Williamson et al., 1995) defined on $(-\infty, +\infty)$ as $\log(\psi_{ijj'}) = \Delta_0 + \Delta_j + \Delta_{j'} + \Delta_{jj'} + Z_i^T\alpha_1$, where Δ_0 is intercept, Δ_j is jth level intercept with boundary conditions, i.e., $\Delta_1 = 0, \Delta_{jj'}$ is the symmetric interaction ($\Delta_{jj'} = \Delta_{j'j}$) at (j, j') levels of the pair with boundary condition, i.e., $\Delta_{1j} = \Delta_{j1} = 0, Z_i$ is a vector of subject level covariates, and α_1 is the regression parameter vector for the covariate Z_i.

From Plackett (1965), $F_{ijj'}$ can be solved by the quadratic Eq. (2) in terms of $\psi_{ijj'}, \gamma_{i1j}$ and $\gamma_{i2j'}$ as,

$$F_{ijj'} = \begin{cases} \frac{\left\{1+\left(\gamma_{i1j}+\gamma_{i2j'}\right)\left(\psi_{ijj'}-1\right)-\sqrt{Q_{ijj'}}\right\}}{2\left(\psi_{ijj'}-1\right)} & \text{if } \psi_{ijj'} \neq 1 \\ \gamma_{i1j}\gamma_{i2j'} & \text{if } \psi_{ijj'} = 1 \end{cases}, \tag{3}$$

where $Q_{ijj'} = \left\{1 + \left(\gamma_{i1j} + \gamma_{i2j'}\right)\left(\psi_{ijj'} - 1\right)\right\}^2 + 4\psi_{ijj'}\left(1 - \psi_{ijj'}\right)\gamma_{i1j}\gamma_{i2j'}$, for $i = 1, \ldots, N$ and $j, j' = 1, \ldots, K$. The joint cell probability $\omega_{ijj'} = \Pr(Y_{i1j} = 1, Y_{i2j'} = 1)$ can now be calculated by the bivariate cumulative probabilities $F_{ijj'}$'s as $\omega_{ijj'} = F_{ijj'} - F_{ij-1j'} - F_{ijj'-1} + F_{ij-1j'-1}$, for $i = 1, \ldots, N$ and $j, j' = 1, \ldots, K$, with usual boundary conditions for $F_{ijj'}$, when $j = 0, K$ or $j' = 0, K$. This implies that we can write the joint cell probability, $\omega_{ijj'}$, as a function of the marginal cumulative probabilities and the global odds ratios.

3.2 Generalized estimating equations method

Here, we briefly describe the GEE method by Williamson et al. (1995). Let β and α be the mean and association parameters, respectively. Let $Y_i = \left(Y_{i1}^T, Y_{i2}^T\right)^T$ and $\pi_i = \left(\pi_{i1}^T, \pi_{i2}^T\right)^T$ where $Y_{it} = \left(Y_{it1}, \ldots, Y_{itK-1}\right)^T$ and $\pi_{it} = \left(\pi_{it1}, \ldots, \pi_{itK-1}\right)^T$ for $t = 1, 2$. The mean model is the model of (1). For the mean parameter estimation, we solve the first set of estimating equations,

$$S_1(\beta, \alpha) = \sum_{i=1}^{N} D_i^T V_i^{-1}(Y_i - \pi_i) = 0, \tag{4}$$

where $D_i = \partial\pi_i(\beta)/\partial\beta^T$, and V_i is the working covariance matrix of Y_i, which is a function of the parameter β and α, and approximates $\mathrm{Var}(Y_i)$. The matrix V_i is a block matrix,

$$V_i = \begin{pmatrix} V_{i11} & V_{i12} \\ V_{i21} & V_{i22} \end{pmatrix},$$

where $V_{itt} = \text{diag}(\pi_{it}) - \pi_{it}\pi_{it}^T$ for $t = 1,2$ are $(K-1) \times (K-1)$ multinomial covariance matrices of the left and right eye responses, respectively, for individual i. The off-diagonal block matrix $V_{i12}^T = V_{i21} = V_{i21}(\beta, \alpha)$ is a $(K-1)\times(K-1)$ covariance matrix of the responses between two eyes of an individual, with (j, j') element $\text{Cov}(Y_{i1j}, Y_{i2j'}) = E(Y_{i1j}Y_{i2j'}) - E(Y_{i1j})E(Y_{i2j'}) = \omega_{ijj'} - \pi_{i1j}\pi_{i2j'}$.

Let $U_i^T = (U_{i11}, \ldots, U_{i1K}, U_{i21}, \ldots, U_{iKK-1})$ and $\omega_i^T = (\omega_{i11}, \ldots, \omega_{i1K}, \omega_{i21}, \ldots, \omega_{iKK-1})$, where $U_{ijj'} = Y_{i1j}Y_{i2j'}$ has the expectation $E(U_{ijj'}) = \Pr(U_{ijj'} = 1) = \omega_{ijj'}$ and U_i and ω_i are $K^2 - 1$ dimensional vectors. To estimate the parameters of the global odds ratio model, we solve the second set of estimating equations,

$$S_2(\beta, \alpha) = \sum_{i=1}^{N} C_i^T G_i^{-1}(U_i - \omega_i) = 0, \tag{5}$$

where $C_i = \partial\omega_i / \partial\alpha^T$ and $G_i = \text{Var}(U_i) = \text{diag}(\omega_i) - \omega_i\omega_i^T$. A Fisher-scoring type algorithm will be employed to solve the two sets of estimating equations through back-and-forth iteration, $S_1(\beta, \alpha) = 0$ and $S_2(\beta, \alpha) = 0$, for estimating β and α. The robust and model-based variance estimates of $\hat{\beta}$ and $\hat{\alpha}$ are calculated (Lipsitz et al., 1991; Williamson et al., 1995). If true mean model is assumed, the two variance estimates are close when the association model is close to the true model. Note that GEE method gives consistent estimates for the mean parameters, only if the mean model is correct, irrespective of correct specifications of the association model, i.e., robust to the assumption of higher order moments, though the GEE method would lose efficiency since it only uses marginal information in the mean parameter estimation and is not likelihood based.

3.3 Bivariate maximum likelihood method

In the bivariate ML method (Dale 1986), the log-likelihood is a multinomial likelihood and can be written $l(\beta, \alpha) = \sum_{i=1}^{N}\sum_{j=1}^{K}\sum_{j'=1}^{K} U_{ijj'} \log \omega_{ijj'}(\gamma_{i1j}, \gamma_{i2j'}, \psi_{ijj'})$, where ω's are the functions of $\xi^T = (\beta^T, \alpha^T)$ through γ's and ψ's. We call this fixed effect ML model a classical ML model since the models for both mean and association are fully specified. The score equation can be expressed as (McCullagh and Nelder, 1989),

$$S(\xi) = \frac{\partial l}{\partial \xi} = \sum_{i=1}^{N} E_i^T G_i^{-1}(U_i - \omega_i) = 0, \tag{6}$$

where $E_i = \partial\omega_i / \partial\xi^T$. The estimate of ξcan be obtained by solving the score equation with Fisher-scoring algorithm. When all $\psi_{ijj'} = 1$, the GEE method, Eq. (4), and the ML score Eq. (6) coincide and are called the independence estimating equations (IEE's). Note that the classical ML method gives consistent

and fully efficient estimates only when true models for both mean and association are assumed but correct specifications for both mean and association models are usually difficult.

3.4 Univariate worse-eye method

Let $M_i = \max(PS_{i1}, PS_{i2})$ be the worse-eye outcome of a subject i. Assume proportional odds model for $\Gamma_{ij} = \Pr(M_i \leq j \,|X_i) = F_{ijj}$:

$$\text{logit}(\Gamma_{ij}) = \log\left(\frac{\Gamma_{ij}}{1-\Gamma_{ij}}\right) = \delta_j - X_i^T \beta_2, \tag{7}$$

where $\delta_j, j = 1, \ldots, K-1$ is cutoff point parameter, X_i is a subject level covariate vector, and β_2 is a regression parameter vector. Since cataract is an irreversible lens disease, the outcome of the worst eye can be seen as the response of the subject or the subject level response. The parameter vector β_2 can be thought of as the subject level regression parameter vector. This is a multinomial generalized linear model (McCullagh and Nelder, 1989) and can be fit by common software like STATA and SAS.

3.5 Model selection

In the mean model selection, two model selection criteria, AIC (Akaike, 1973) for the likelihood method and QIC (Pan, 2001) for the GEE method, are used,

$$\text{AIC} = -2 \times \log \text{likelihood} + 2 \times p, \tag{8}$$

where p is the total number of parameters in the model and

$$\text{QIC}(R) = -2 \times QL\left(\hat{\beta}\right) + 2 \times \text{trace}\left(\hat{\Omega}_I \hat{V}_R\right), \tag{9}$$

where $\hat{\beta}$ is the GEE mean parameter estimate, $QL\left(\hat{\beta}\right)$ is log-likelihood for independence model, i.e., multinomial likelihood, evaluated at $\hat{\beta}$, $\hat{\Omega}_I$ is the inverse of the model-based variance of $\hat{\beta}$ in the independence model evaluated at $\hat{\beta}$, and $\hat{V}_R$ is the robust variance estimate of $\hat{\beta}$ in the GEE.

QIC(R) is the model selection criterion for GEE based on the non-independence association model, whereas later we use QIC(Ind) criterion, which is a QIC model selection criterion based on IEE. Since IEE is a likelihood-based method, we can use AIC as well. However, since the IEE model is possibly the wrong model for our data set and QIC(Ind) takes into consideration the difference between model-based and robust variances, we need to use QIC(Ind) instead of AIC, which was suggested by Pan (2001).

4 Application

We apply the methods described in the Statistical methods section to the complete PS data of atomic-bomb survivors in Hiroshima and Nagasaki, assuming symmetric response probabilities between left and right eyes. The basic main effect model for the mean is $\text{logit}(P_{ij}) = \kappa_j - \tau_C C - \tau_S S - \tau_B B - \tau_D D$, where $P_{ij} = \gamma_{i1j} = \gamma_{i2j}$ or $P_{ij} = \Gamma_{ij}, C$ is city variable (zero for Hiroshima and one for Nagasaki), S is sex variable (zero for male and one for female), $B =$ (age at exposure $- 10)/10$ is birth cohort variable, and D is the DS02 eye radiation dose (Sv). κ_j's are the cutoff points for $j = 1, \ldots, K-1 = 4$ and τ's are the regression parameters. We will denote the above mean model as $C + S + B + D$. In GEE application, we assumed a simple constant global odds ratio association model, $\log(\psi_{ijj'}) = \Delta_0$ as suggested by Lumley (1996) and O'Hara Hines (1997).

The full mean model is $C+S+B+D+CS+CB+SB+CD+SD+BD$, where CS stands for sex by city interaction, CB for birth cohort by city interaction, SB for birth cohort by sex interaction, CD for dose by city interaction, SD for dose by sex interaction, and BD for dose by birth cohort interaction. The above full model comprised subject level covariates since one can assume risks of lens opacity to be symmetric between left and right eyes. Model selection was made among all hierarchical sub-models of the full model, where the model is said to be hierarchical if an interaction is included in the model, then the main effects are included in the model as well.

In the mean model selection, since the data distribution is highly skewed in radiation dose and more than two-thirds of the subjects are in the low dose range (<0.5 Sv), the background model selection with whole data was made without radiation dose term. The full background model is $C + S + B + CS + CB + SB$. There are 18 hierarchical sub-models. Among them, the nearly best background models, including the best background model, were selected by AIC or QIC criteria. Next, the best model with dose terms was selected by AIC or QIC model selection criteria. By this procedure, the best dose response model would be selected. All significance tests were by two-sided Wald test. STATA and GAUSS software packages were used for all computations.

The best model for univariate analysis is $C + S + B + D + BD$, as indicated in Table 2. The dose effect was highly significant ($p < 0.001$). The dose by birth cohort interaction was significant ($p = 0.020$). The IEE and GEE best model selected by QIC(Ind) and QIC(R) criteria, respectively, are the same as the best univariate model. Table 3 shows the IEE best model selected by QIC(Ind) criterion. Table 4 shows the GEE best model selected by QIC(R) criterion. The dose effect was again highly significant ($p < 0.001$) for IEE and GEE analyses and p-values of dose by birth cohort interaction were 0.017 for IEE analysis and 0.016 for GEE analysis. The global odds intercept estimate was about 3.64, which implies a global odds ratio estimate of 38.1. The IEE and GEE robust standard errors (SE's) are slightly smaller than the univariate SE's. The difference between robust and model-based SE's is large in IEE but small in GEE.

Table 2 Parameter estimates of the AIC best model in univariate analysis of PS using worse-eye method (cutoff point parameters are excluded)

Variable	Estimate	Std error	Odds ratio	2-sided p*
City (Naga/Hiro)	0.479	0.180	1.61	0.008
Sex (fem/male)	0.376	0.183	1.46	0.039
B: (age_at_exp-10)/10	1.089	0.159	2.97	<0.001
Dose	0.375	0.097	1.45	<0.001
B×Dose	−0.299	0.129	0.74	0.020

*Wald test; AIC = 1042.2

Table 3 IEE best model selected by QIC(Ind) for PS data (cutoff point parameters are excluded)

Variable	Estimate	Std error[a]	Odds ratio	2-sided p*
City (Naga/Hiro)	0.518	0.177 (0.135)	1.68	0.003
Sex (fem/male)	0.330	0.180 (0.138)	1.39	0.067
B: (age_at_exp-10)/10	1.064	0.157 (0.119)	2.90	<0.001
Dose	0.445	0.090 (0.074)	1.56	<0.001
B×Dose	−0.294	0.123 (0.096)	0.75	0.017

[a] Robust standard error (model-based standard error)

* Wald test using robust standard error; QIC(Ind) = 1745.8

Table 4 GEE best model selected by QIC(R) for PS data (cutoff point parameters are excluded)

Variable	Estimate	Std error[a]	Odds ratio	2-sided p*
City (Naga/Hiro)	0.518	0.177 (0.176)	1.68	0.004
Sex (fem/male)	0.327	0.180 (0.179)	1.39	0.069
B: (age_at_exp-10)/10	1.072	0.157 (0.155)	2.92	<0.001
Dose	0.445	0.090 (0.097)	1.56	<0.001
B×Dose	−0.296	0.123 (0.127)	0.74	0.016

[a] Robust standard error (model-based standard error)

* Wald test using robust standard error; log of association parameter estimate = 3.64 (robust SE = 0.245); QIC(R) = 1502.1

The robust SE's are exactly the same in both the IEE and GEE analyses. The risks in the tables show that the three methods provide nearly equal results.

We modeled the association of bivariate response in GEE analysis in other ways, with $\log\left(\psi_{ijj'}\right) = \Delta_0 + \alpha_C C + \alpha_S S + \alpha_B B + \alpha_D D$, and the symmetric exchangeable association model $\log\left(\psi_{ijj'}\right) = \Delta_0 + \Delta_j + \Delta_{j'} + \Delta_{jj'}$ with 15 parameters. With the best mean model, QIC(R) was 1494.3 for the first association model and 1478.8 for the second symmetric exchangeable association model, whose QIC(R) values are smaller than the QIC(R) value of 1502.1 given in Table 4. This is because QIC(R) did not take into account the number of parameters in the association model. However, once again the robust SE's for the mean parameter estimates did not differ at all among the two association models and were almost equal to those presented in Tables 3 and 4. At least in the present

bivariate polytomous data, the complication of association improved the QIC; however, the complication did not at all improve the estimation efficiency.

5 Considerations for bias

If we assume the symmetric marginal response probabilities $\gamma_{ij} = \gamma_{i1j} = \gamma_{i2j}$ for $j = 1, \ldots, K-1$ in the left and right eyes, then, from formula (3), the probability distribution of univariate response using the worse-eye method, $M_i = \max(PS_{i1}, PS_{i2})$, is, neglecting suffix i,

$$\Pr(M \le j) = \Gamma_j = \gamma_j + \frac{1 - \sqrt{Q_{jj}}}{2(\psi_{jj} - 1)}, \tag{10}$$

where $Q_{jj} = \{1 + 2\gamma_j(\psi_{jj} - 1)\}^2 + 4\psi_{jj}(1 - \psi_{jj})\gamma_j^2 = 1 + 4(\psi_{jj} - 1)\gamma_j(1 - \gamma_j)$. The true response probability is thought to be the bivariate marginal probability γ_j, while the univariate probability Γ_j approximates γ_j. Therefore, a bias of the dose response parameter in Γ_j compared with the one in γ_j can be considered. Figure 1 describes the transformation curve between Γ_j and γ_j at various values of the constant global odds ratio association $\psi_{jj} = \psi$. When $\psi = 1$, i.e., left and right eyes are independent, then $\Gamma_j = \gamma_j^2$, and when ψ tends toward ∞, then $\Gamma_j = \gamma_j$; that is, when ψ is very large, modeling $\Gamma_j = \Pr(M \le j)$ is equivalent to modeling $\gamma_j = \Pr(PS_1 \le j) = PR(PS_2 \le j)$, which results in an identical model in both univariate and bivariate analyses. In our situation, the estimate of ψ is about 38.1, resulting in $\Gamma_j \approx \gamma_j$, as shown in Fig. 1. Some bias in the parameter estimate is, however, caused by the curvature between Γ_j and γ_j when ψ is finite. When ψ is smaller, however, the bias becomes larger in the univariate analysis.

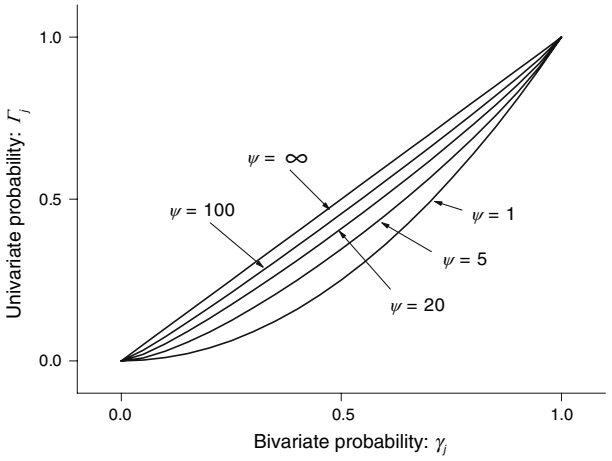

Fig. 1 Relationship between univariate response probability Γ_j and bivariate response probability γ_j at various values of global odds ratio

We can calculate bias in the linear predictor of the univariate response probability $\Gamma = \text{logit}^{-1}(\delta + \beta_2 D)$ compared with that of bivariate marginal probability $\gamma = \text{logit}^{-1}(\theta + \beta_1 D)$ in the binary case, as indicated in the Appendix. The left panel in Fig. 2 shows the bias in terms of radiation dose, where the example model is $\text{logit}(\gamma) = -1.386 - 0.4D$, with background prevalence 0.2 and odds ratio per Sv = 1/1.5. There are negative biases in intercept and slope in all cases; however, when ψ is large, the negative slope bias is small. The right panel in Fig. 2 shows the bias in terms of radiation dose, where the example model is $\text{logit}(\gamma) = -1.386 + 0.4D$, with background prevalence 0.2 and odds ratio per Sv = 1.5. There are negative biases in intercept and positive biases in slope in all cases; however, when ψ is large, the positive slope bias is small. In both cases above, the logit of Γ is approximately linear in dose D, though the univariate dose response parameter β_2 is exaggerated compared with bivariate parameter β_1. If the background prevalence is 0.9, these biases are very slight or non-existent, irrespective of the value of the association and the sign of the slopes. When $\gamma \approx 0.5$, we can derive the relationship between the dose response parameters β_2 and β_1 as (see Appendix),

$$\beta_2 \approx \beta_1 \frac{\left(1 + \sqrt{\psi}\right)^2}{\sqrt{\psi}\left(2 + \sqrt{\psi}\right)}. \tag{11}$$

Thus, β_2 is exaggerated when compared with β_1, since the factor is always greater than one. The bias is less than 33% if $\psi \geq 1$, and when global odds ratio is greater than 30, the bias is smaller than 3%. Note that in a mean model with various continuous and indicator independent variables, the biases can

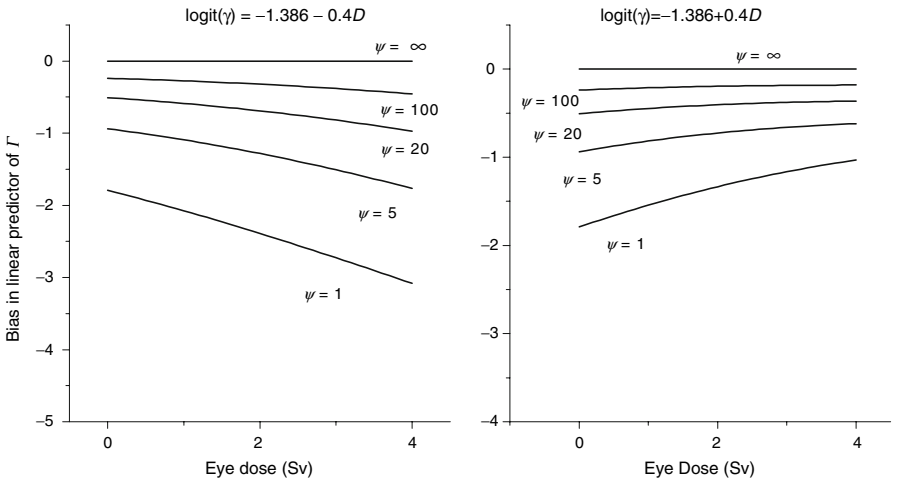

Fig. 2 Bias in linear predictor in univariate analysis compared with bivariate analysis for binary cases in various global odds ratio ψ, with background prevalence of 0.2 and the odds ratios per Sv in dose response 1/1.5 for the *left panel* and 1.5 for the *right panel*

be serious or result in a totally different model in model selection when the association is small.

6 Standard errors and wald statistics

Simulation studies were made under the assumption of a bivariate ordered trinomial setting. The model is $\text{logit}(\gamma_{tj}) = \theta_j + 2.0X$ for $t = 1, 2$ with cutoff points $\theta_1 = -1.0, \theta_2 = 0.5$ and a slope 2.0 for a subject level covariate X being uniformly distributed covariate on (0, 1). A constant GOR was assumed. The sample size was 1,000, which is a large sample. The upper panel in Fig. 3 shows the ratios of SE's relative to the ML model-based SE, which is the correct SE. Below a GOR of 20, the univariate SE is inflated more than about 10% compared with the ML model-based SE. The IEE model-based SE provides

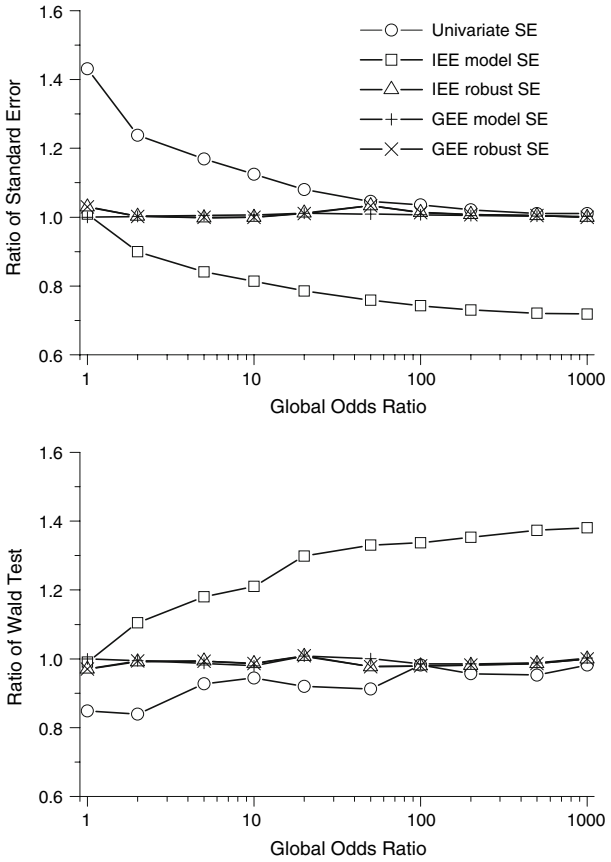

Fig. 3 Ratio of standard errors (*upper panel*) and ratio of Wald test (*lower panel*) of various methods relative to ML model standard error and the Wald test, respectively, with bivariate trinomial data generated under the model $\text{logit}(\gamma_{tj}) = \theta_j + 2.0X; \theta_1 = -1.0, \theta_2 = 0.5$ for $t = 1, 2$ with constant GOR and sample size = 1,000. The model SE indicates the model-based SE

a smaller SE than the correct SE, which results in Type I error rate becoming larger than the nominal level. Interestingly, the IEE method with robust SE, and GEE method with model-based and robust SE were almost fully efficient in parameter estimation in all ranges of GOR in these simulations.

The lower panel in Fig. 3 gives the ratios of Wald statistics relative to the statistics based on ML model SE, or the correct Wald test statistics. The univariate Wald test statistic is somewhat conservative in the small range of GOR. The Wald test statistics based on IEE model-based SE are always liberal with inflated Type I error rate. The IEE Wald test based on robust SE, and the GEE Wald test based on model-based and robust SE's are correct Wald tests. In both standard errors and Wald statistics shown in Fig. 3, the IEE method with robust SE is useful, though the IEE is a simpler method.

We considered the case when GOR association between left and right eyes depends on a covariate. The IEE robust SE, and GEE model-based and robust SE performed similarly well, as shown in Fig. 3, irrespective of whether the covariate in GOR was in the mean or not and the level of response, K. The Wald test statistics also performed similarly well, the same way as shown in Fig. 3.

Under the non-symmetric model $\text{logit}(\gamma_{tj}) = \theta_j + 2.0X + 0.7(t-1)$ for $t = 1, 2$ with $\theta_1 = -1.0, \theta_2 = 0.5$ and a constant GOR, we also performed a simulation to confirm the performance of SE for the estimates of a subject level covariate, X, and a within subject level covariate, $t - 1$. The IEE method with robust SE, and GEE method with model-based and robust SE were highly efficient in parameter estimation in the smaller GOR range i.e., less than 50. When GOR became larger, we saw a slight discrepancy between the GEE model-based and robust SE's. A slight efficiency loss of the robust SE was observed for both subject level covariates and within subject level covariates. We made a similar simulation study of the sample size 500. The performance of the SE's and Wald statistics were almost similar to the case of sample size 1,000.

7 Discussion

A number of methods exist for combining outcomes from both eyes into a single person-level outcome. Gange et al. (1995) used the composite response method in investigating diabetic retinopathy. The researchers produced a $2K - 1$ level univariate response from K level bivariate responses and applied a proportional odds model to the univariate response. Thus, the method they developed differs from ours in that it combines a bivariate response into a univariate response. However, we think our method is more natural and convenient. Gange et al. (1995) compared the GEE method for bivariate analysis based on correlation with the analysis using a composite method, and concluded that when there are only person level covariates it is appropriate to use the composite response method. In the present lens opacity data, we came to the same conclusion for our univariate method.

Gange et al. (1995) showed the bias of regression parameters of the composite response method compared with the bivariate GEE method in a binary case. We can derive the bias in terms of correlation, ρ, of bivariate outcomes since we have a relationship $\psi = \left(\frac{1+\rho}{1-\rho}\right)^2$ at $\gamma \approx 0.5$. We then obtain the relationship,

$$\beta_1 \frac{\left(1+\sqrt{\psi}\right)^2}{\sqrt{\psi}\left(2+\sqrt{\psi}\right)} = \beta_1 \left(\frac{1}{1+\rho} + \frac{1}{3-\rho}\right), \tag{12}$$

at $\gamma \approx 0.5$, the right-hand formula of which is given by Gange et al. (1995). In polytomous cases, i.e., when the number of the response level is greater than or equal to 3, the regression parameter of the proportional odds model shown in formula (1) is a common combined parameter of the $K-1$ parameters of the binary logistic model for $K-1$ sets of new binary data, which are produced in giving zero for the response greater than or equal to j and one for the response less than j for $j = 2, 3, \ldots, K$. Thus, the result of the bias for the binary model discussed in Sect. 5 is applicable to the polytomous case. That is, the fact that univariate analysis exaggerates the parameter is also true for the polytomous case although if GOR is large, e.g., GOR > 30, the bias is small.

The results of the simulation comparison of SE's and Wald statistics, Fig. 3, were similar to results by Gange et al. (1995). However, we made comparisons with the ML method, the points of which differ from the comparison by Gange et al. (1995). In addition to the fact that the GEE method is consistent and robust to the assumption of higher order moment, it is notable that, when only subject level covariates are included in the mean model, efficiency loss in the GEE method is little for bivariate qualitative ordered polytomous data analysis. The bivariate IEE with robust SE and GEE with model-based or robust SE are recommended instead of univariate analysis when the association is small or within subject level covariates are included in the mean model. Our bivariate ML model is a classical fixed effect model and the model is fully specified. Therefore, model checking is possible, while, with the GEE method, the model checking is probably impossible or difficult (Lee and Nelder, 2004) because only the marginal means are specified. The GEE method has a defect in model checking, but in mean parameter estimation it is superior to the classical ML method.

Among 730 subjects, 28 were examined in only one eye, and 39 subjects were not examined in both eyes. Unbalanced data were obtained when the photograph was out of focus, irrespective of the degree of lens opacity, which indicates that the missing data mechanism is missing completely at random (Diggle et al. 2002). The missing data can be easily handled with the GEE method, since GEE uses only marginal responses. But our univariate and bivariate ML methods cannot cope with missing responses since $M_i = \max(PS_{i1}, PS_{i2})$ and $U_{ijj'} = Y_{i1j}Y_{i2j'}$ are not determined and become missing when one of the lens opacities of both eyes is missing. The GEE method therefore is superior to our ML method in treating the unbalanced data. From chap. 13 in Diggle et al. (2002), if the miss-

ing data mechanism is at random, i.e., missing at random (MAR) or missing completely at random (MCAR), then the joint density of the observed response and the missing response indicator can be written without the missing response. Under MCAR, the observed response $Y^{(o)}$ and the missing response indicator R are independent, the joint density can be expressed as $f(y^{(o)}, r) = f_1(r)f_2(y^{(o)})$ with the marginal densities f_1 and f_2 for variables R and $Y^{(o)}$, respectively, and we put $E(Y^{(o)}) = \mu$. Under MAR, a weaker condition than that of MCAR, the joint density is expressed as $f(r, y^{(o)}) = f_{1|2}(r\,|y^{(o)})f_2(y^{(o)})$ with $f_{1|2}$ being the conditional density of R given $Y^{(o)}$, in which the two variables are not independent, and in this case $E(Y^{(o)}) \neq \mu$. These imply the following two points. The mean–variance relationship in the first set of GEE (4) indicates that the missing data mechanism is implicitly assumed to be MCAR. If the missing data mechanism is MAR, then the mean and the working variance in GEE have to be adjusted for bias, taking the missing data mechanism into consideration. On the other hand, with the likelihood method, if the missing data mechanism is at least MAR, we expect no bias in the parameter and little or no loss of information in the estimation (Diggle et al., 2002). The discussion above indicates that there is a tradeoff between GEE and our likelihood methods in terms of handling of the missing data and assumption of the missing data mechanism.

In the current GEE analysis, there was a marginally significant positive side effect ($p = 0.041$), which is the common difference between cutoff points of left and right eye responses, with left eye response being baseline. We assumed the model, except side effect variable, was the same as the present best model, i.e., $T + C + S + B + D + BD$ in our notation with $\mathrm{QIC}(R) = 1498.7$, where T stands for side effect. The data suggest that the right eye PS is a lower opacity grade than the left eye PS. Everyone has one dominant eye. We suspect that this dominance was the cause of the side effect in our analysis. That is, the dominant eye is less affected by posterior sub-capsular lens opacity. The GOR associations of bivariate data for NC, NO and CC were larger than that of PS and were 201, 175, and 42, respectively. The results from univariate and bivariate analyses in terms of subject level covariates coincided and are shown in Nakashima et al. (2006).

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Appendix

In the binary case, Γ can be written as $\Gamma = \gamma + h(\gamma, \psi)$, where $h(\gamma, \psi) = 0$ if $\psi = \infty; h(\gamma, \psi) = \left\{1 - \sqrt{1 + 4(\psi - 1)\gamma(1 - \gamma)}\right\}/\{2(\psi - 1)\}$ if $1 < \psi < \infty$ and

$h(\gamma, \psi) = -\gamma(1-\gamma)$ if $\psi = 1$. We then have $\frac{\Gamma}{1-\Gamma} = \frac{\gamma}{1-\gamma}\frac{1+h/\gamma}{1-h/(1-\gamma)}$. The bias of the linear predictor $B = \text{logit}(\Gamma) - \text{logit}(\gamma) = \log\left\{\frac{1+h/\gamma}{1-h/(1-\gamma)}\right\}$ is a function of γ and ψ. The bias of the slope parameter can be calculated as $\frac{\partial B}{\partial D}$. The relative bias of the slope parameter is approximately $\frac{1}{\sqrt{\psi}(2+\sqrt{\psi})}$ when $\gamma \approx 0.5$.

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