Appropriate Statistical Methods to Account for Similarities in Binary Outcomes Between Fellow Eyes

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Purpose. Many ocular measurements are more alike between fellow eyes than between eyes from different individuals. To make appropriate inferences using data from both eyes rather than the best or worst eye, statistical methods that account for the association between fellow eyes must be used.

Methods. Marginal and conditional regression models account for the association between fellow eyes in different ways. The authors compare and contrast these methods using data from a series of patients with retinitis pigmentosa in whom the primary object is to identify risk factors, some of which are subject specific and some of which are eye specific, for visual acuity loss (as a binary outcome) among affected subjects.

Results. Odds ratios for age, gender, presence of posterior subcapsular cataract, and genetic type of retinitis pigmentosa obtained from the marginal model were all larger than those from the conditional model. Familial aggregation of visual acuity loss was statistically significant in the marginal, but not in the conditional, model.

Conclusions. The estimates and interpretation of the association between an ocular outcome and risk factors can differ significantly between these two approaches. The choice of model depends on the scientific questions of interest rather than on statistical considerations. Computer programs are available for implementing both models. Invest Ophthalmol Vis Sci. 1994;35:2461-2465.

Most ocular measurements are more alike between fellow eyes than between eyes of different individuals. Examples would be intraocular pressure, visual acuity, refractive error, and optic disk morphology. This can be due to structural similarities between fellow eyes, genetic predispositions to certain diseases, or the systemic source of many bilateral ocular disorders. In studies of ocular disorders or treatment effects, measurements are usually available on both eyes of an individual. Two basic approaches to data analysis are available. Subjects can be classified according to their best or worst eye, one eye can be selected at random for analysis, or measurements from both eyes can be averaged. This approach is relatively simple and scientifically valid in situations in which visual function is driven by the outcome in the best (or worst) eye and all dependent variables of interest are subject specific. Alternatively, the data from both eyes can be included in the analysis, increasing the power to detect differences and improving the precision of regression coefficient estimates. In addition, it may be of scientific interest to examine the association between eye-specific risk factors and visual outcome for each eye separately. In these situations, it is appropriate to include data from both eyes in the analysis. When similarities exist between eyes, the measurements from fellow eyes cannot be treated as if they were independent, that is, as if they were measurements from eyes of different individuals. The similarities between eyes must be taken into account when weighing the evidence in ocular data. Failure to do so will lead to invalid inferences, the degree of error depending on the similarity or correlation between eyes. This correlation can be large. For example, the correlations of intraocular pressure, cup-to-disc ratio, and threshold sensitivity between fellow eyes has been estimated to be 0.81, 0.84, and 0.79, respectively. The need to account for
correlation has been recognized by ophthalmic researchers, and solutions that address specific data analyses have been proposed.1-5

Regression analysis is an appropriate statistical method for examining the dependence of an ocular outcome on risk factors. An example might be the risk of glaucoma and its dependence on age, intraocular pressure, and systemic hypertension. Several statistical methods for regression that take appropriate account of correlation among the outcome variable have been developed recently, and several have been applied to the specific ophthalmic problem of correlation between fellow eyes.6-11 Methods exist for continuous outcomes, such as intraocular pressure, and for binary responses, such as whether or not the eye has a cataract. These methods estimate the strength of the relationship between the outcome and the risk factors and the degree of uncertainty surrounding this relationship, while appropriately taking into account the magnitude of the correlation between fellow eyes.

The regression results for several of these methods were recently compared to each other and to methods that did not adjust for correlation using the same data sets.12 The two analytic approaches that adjusted for correlation between eyes resulted in appropriate standard errors that were often larger than if correlation between eyes was ignored. In the data set with a binary outcome, different regression coefficients and standard errors, but comparable P values, were obtained with the two different approaches. Although these methods adjust for the correlation between fellow eyes, they are designed to estimate different quantities and, therefore, to address different scientific questions. Hence, there is no a priori reason to expect similar results. In this paper, we discuss and illustrate the differences between two of the regression approaches using visual acuity data from a series of patients with retinitis pigmentosa.

**METHODS**

There are two general approaches to analyzing ocular data in which the outcome in fellow eyes is correlated, and one wishes to estimate the relationship between the outcome and a set of risk factors (regression analysis).11,13-10 One approach is to model the outcome in one eye as a function of the risk factors and, simultaneously, to model the outcome in the fellow eye. We call this a conditional model because the outcome in one eye is conditioned, or adjusted, for the outcome in the fellow eye.8,17-10 Another approach is to model the outcome in each eye as a function of the risk factors and to model separately the correlation between the fellow eyes. We term this a marginal model.9,10 Both approaches provide estimates of the probability that both eyes are affected and both can apply to outcomes that are either continuous (e.g., intraocular pressure) or binary (e.g., presence or absence of glaucoma). We present here the formulation of models for binary data because we would like to illustrate the main ideas and because the example that follows has a binary outcome.

Logistic regression is the most commonly used method for studying the relationship of a binary outcome Y with explanatory variables X1, . . . , Xp. Given data on only one eye per person, the logistic model can be expressed as

\[
\log \frac{Pr(Y = 1)}{Pr(Y = 0)} = \beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p. \tag{1}
\]

That is, the model assumes the logarithm of the odds of a positive outcome (Y = 1) is a linear function of each of the explanatory variables, X1, . . . , Xp. To make it simpler, we write the right hand side as \(X \beta\).

The conditional model for the responses YR and YL for the right and left eyes can be written as follows:

\[
\log \frac{Pr(Y_R = 1 | Y_L)}{Pr(Y_R = 0 | Y_L)} = X_R \beta^* + \delta Y_L \tag{2}
\]

\[
\log \frac{Pr(Y_L = 1 | Y_R)}{Pr(Y_L = 0 | Y_R)} = X_L \beta^* + \delta Y_R \tag{2}
\]

where YR and YL are the outcomes in the right and left eyes, respectively, X_R and X_L are the explanatory variables for the right and left eyes, \(\beta^*\) are the associated regression coefficients, and \(\delta\) measures the association between fellow eyes. Note the notation \(Pr(Y_L | Y_R)\) represents the probability of Y_L = 1 given the observed value of Y_R. The conditional model expresses the log odds that Y_R or Y_L equal 1 as a simple function of both the explanatory variables and the response for the other eye. That is, the value for the other eye is treated as another explanatory variable. The interpretation of \(\beta^*\) above is, therefore, the effect of X_R on Y_R that cannot be attributed to Y_L. The conditional model attributes to the explanatory variables what cannot be explained by the response in the other eye.

The marginal approach does not include the other eye as one of the explanatory variables but accounts for the association between eyes by adding a second equation for this association to the ordinary logistic regression given in equation 1. The marginal model can be written as follows:

\[
\log \frac{Pr(Y_R = 1)}{Pr(Y_R = 0)} = X_R \beta \tag{3}
\]

\[
\log \frac{Pr(Y_L = 1)}{Pr(Y_L = 0)} = X_L \beta \tag{3}
\]

\[
\log \text{OR} (Y_R, Y_L) = Z \alpha \tag{3}
\]
where \( Y_R \) and \( Y_L \) are the outcomes in the right and left eyes, respectively, \( X_R \) and \( X_L \) are the explanatory variables for the right and left eyes, \( \beta \) are the regression coefficients for the marginal model, and \( Z \) measures the association between fellow eyes (\( Z \) are explanatory variables that represent the association between fellow eyes). Here, \( \beta \) has the same interpretation as if only one eye per person was used. If only one eye is available for each person, the marginal model simplifies to ordinary logistic regression. It describes the relationship of the response with the explanatory variables without regard for the other eye. The log odds ratio expresses the association between the two eyes as a linear function of the explanatory variables, \( Z \). The odds ratio between \( Y_R \) and \( Y_L \) is the ratio of the odds that \( Y_R = 1 \), given \( Y_L = 1 \) versus \( Y_L = 0 \) or, equivalently, that \( Y_L = 1 \) given \( Y_R = 1 \) versus \( Y_R = 0 \).

\[
\text{OR}(Y_R, Y_L) = \frac{\Pr(Y_R = 1 \mid Y_L = 1)/\Pr(Y_R = 0 \mid Y_L = 1)}{\Pr(Y_R = 1 \mid Y_L = 0)/\Pr(Y_R = 0 \mid Y_L = 0)} = \frac{\Pr(Y_L = 1 \mid Y_R = 1)/\Pr(Y_L = 0 \mid Y_R = 1)}{\Pr(Y_L = 1 \mid Y_R = 0)/\Pr(Y_L = 0 \mid Y_R = 0)} \tag{4}
\]

We illustrate the differences between the marginal and the conditional models using data on a series of patients with retinitis pigmentosa. Analyses of these data that account for the correlation between eyes using several different methods have been reported. These data were analyzed using the marginal and conditional approaches, and the odds ratios and associated \( P \) values obtained from the two approaches were compared. These data have two nested levels of clustering, eyes within people and people within families. Hence, the models must account for the association between two eyes of the same person, between different members of the same family and between persons in different families. In the marginal model, only the equation for the odds ratio must be changed. The covariates \( Z \) would include binary variables indicating the type of pair (same person–different eyes, same family–different persons). The conditional model changes more dramatically, now describing the conditional distribution of an eye given the outcome for its pair as well as the outcomes for all other eyes in the family.

A total of 1,038 eyes of 519 subjects in 444 families were enrolled in this study. Of interest was whether poor visual acuity depended on the genetic type of retinitis pigmentosa after adjusting for age, gender, and the presence of a posterior subcapsular cataract. Also of interest was whether poor visual acuity clustered within affected family members, and whether poor visual acuity in one eye was associated with poor acuity in the fellow eye of affected individuals. The outcome variable was whether an eye had visual acuity of 20/50 or worse. Explanatory variables were: age in 10-year groupings, gender, presence of a posterior subcapsular cataract, and genetic type of retinitis pigmentosa. Hence, family-specific, person-specific, and eye-specific explanatory variables were included in the analysis. In each of the models, associations between eyes of the same person and between members of the same family were estimated and compared.

The marginal model was fit using a generalized estimating equation (GEE) program written in C and run under S. A GEE program for fitting these models is also available using an SAS macro (SAS Institute, Cary, NC). There are two GEE approaches. One is more appropriate when the primary question of interest is the association between the outcome and risk factors and in which the association between eyes and between family members needs to be accounted for but is not of interest itself (GEE1). The other is more appropriate when the association between eyes and between family members is also of interest (GEE2). This was the method used in this example. The method that simultaneously estimates maximum likelihood regression parameters and odds ratios between family members and between eyes was used for the conditional approach.

**RESULTS**

The distribution of genetic type of retinitis pigmentosa by family size is given in Table 1. There were 309 subjects who had no other family members with disease. By definition, these are families of size 1, the number of affected family members. There were 27 families in which one member was autosomal dominant, 46 in which one member was autosomal recessive, and 16 families in which one member was X-linked. Some families had more than one affected member; the maximum number was six. Of the 519 subjects in this study, 220 had bilateral visual acuity

**TABLE 1. Distribution of Family Size by Genetic Type of Retinitis Pigmentosa**

<table>
<thead>
<tr>
<th>Family Size</th>
<th>Isolated</th>
<th>Dominant</th>
<th>Recessive</th>
<th>X-linked</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>309</td>
<td>27</td>
<td>46</td>
<td>16</td>
<td>398</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>63</td>
<td>27</td>
<td>444</td>
<td>444</td>
</tr>
</tbody>
</table>
loss, 81 had unilateral loss, and 218 did not have visual acuity worse than 20/50 in either eye. The unadjusted pairwise odds ratio for the association between eyes was 29.2, indicating a strong interocular association of visual acuity loss.

Several differences between the odds ratios obtained from conditional and marginal models were found (Table 2). In general, odds ratios estimated using the conditional model were smaller than those obtained from the marginal model. The odds ratio representing familial aggregation was 1.85 (95% confidence interval: 0.92 to 3.74) for the conditional model. The marginal model gave an odds ratio of 3.30 (95% confidence interval: 1.65 to 6.60). Poor visual acuity was strongly associated within fellow eyes in both models (adjusted odds ratio of 26.29). Logistic regression coefficients obtained from the marginal model for genetic type, age, gender, and presence of a cataract were between 1.21 and 2.39 times larger than those obtained from the conditional model. This translates to odds ratios for the marginal model ranging from 2% to 72% larger than those obtained from the conditional model, with the familial association being 78% larger under the marginal model.

**DISCUSSION**

In both models, the estimates of the association between eyes were similar. However, the familial aggregation was significantly larger in the marginal than in the conditional model. In addition, the association between visual acuity loss and x-linked disease was much larger in the marginal than in the conditional model. Hence, the choice of model can result in different inferences about the association between risk factors and outcome. In this problem, one might expect the magnitude of the associations to be smaller in the conditional than in the marginal model because of the positive correlation of visual acuity between eyes. This was the case for the association between visual acuity and genetic type, cataract, age, and gender. In the conditional model, the association between poor visual acuity in one eye and an explanatory variable such as posterior subcapsular cataract in that eye is partly attributed to the poor visual acuity of the fellow eye. Hence, the association between visual acuity loss and cataract is smaller in the conditional than in the marginal model. In the marginal model, the approach is to model the association between visual acuity and cataract for each eye separately and simultaneously to account for the association between fellow eyes. The tendency for estimates in the conditional model to be smaller than those from the marginal model has been noted in this and other data sets.

The regression coefficients have different interpretations in the two models. The conditional odds ratio estimates the association between poor visual acuity and, for instance, cataract that cannot be explained by poor acuity in the fellow eye. The marginal approach estimates the association between visual acuity loss and cataract in the same eye. The visual acuity loss in the fellow eye is not used to explain some of the association between cataract and visual acuity loss in the same eye. In addition, the interpretation of the regression coefficient also changes with the number of observations per subject. This is particularly relevant when there are family associations because family size can vary substantially. In addition, conditioning on the other family members leads to different regression coefficients and their interpretations for families of different sizes. In the conditional model, those with data on only one eye will contribute to the estimation of the between-eye association only through the regression parameters. In the marginal model, subjects can contribute one or both eyes without any change in the analytic approach or the interpretation of regression coefficients. When only one eye is available for each person, the marginal model simplifies to the ordinary logistic regression model.

Although each model has advantages and disadvantages, the choice of model depends on the scientific question of interest. Concerning whether poor visual acuity in a particular eye is associated with the genetic type of retinitis pigmentosa after adjustment for age, gender, and cataract, the marginal model is more appropriate. Similarly, if one were evaluating a treatment that affected both eyes equally, the treatment effect in the conditional model would be underestimated because some of the treatment effect will be explained by the association of the outcome between eyes. If one were interested in predicting the risk of retinal detachment in an eye after surgery, determin-
ing whether the fellow eye had experienced retinal detachment would be both sensible and important. In this example, the conditional model would be more appropriate. The selection of either the marginal or conditional model that accounts for the correlation between fellow eyes is clearly important. We argue that the selection of a model to adjust for this correlation is dependent upon the scientific question of interest, and that the interpretation of the results can differ with the choice of model.

**Key Words**

ophthalmology, statistics, logistic regression, odds ratio

**References**