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Estimation of the Relative Excess Risk Due to Interaction and Associated Confidence Bounds

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The relative excess risk due to interaction (RERI) provides a useful metric of departure from additivity of effects on a relative risk scale. In this paper, the authors show that RERI is identical to the product term in a linear odds ratio or a linear relative risk model. SAS and STATA codes are provided for fitting a linear odds ratio model that directly parameterizes RERI. In addition, this paper presents a method for obtaining likelihood-based 95% confidence bound estimates for RERI. The authors show that likelihood-based confidence intervals may differ substantially from the asymptotic confidence interval estimates advocated by previous authors. The approach presented in this paper should facilitate estimation of RERI and associated likelihood-based confidence bounds, by using standard statistical packages.

confidence intervals; interaction; logistic regression; risk ratio

Abbreviations: ERR, excess relative risk; RERI, relative excess risk due to interaction; RR, relative risk.

Often, in epidemiologic research, a data analyst is interested in the joint exposure effects of 2 factors on disease risk. Questions regarding the nature of joint effects arise in nearly all areas of epidemiologic study, as investigators consider potential interactions between factors that may be biologic, behavioral, environmental, economic, or psychosocial.

Exponential models are widely used for the analysis of disease rates, risks, and odds (1, pp. 393–398; 2). Under an exponential model, a departure from multiplicativity in the joint effects of 2 factors is readily evaluated by inclusion of a product interaction term in the regression model. This has led to a widespread phenomenon in the epidemiologic literature of authors making statements regarding the absence of evidence of interaction between 2 factors when, more specifically, what they mean is that the data appear to conform to multiplicativity of effects on a relative risk, relative rate, or relative odds scale (1, pp. 74–80).

Rothman and others have noted that an assessment of interaction on an additive scale is often of interest and, in some contexts, is more meaningful than an assessment of interaction on a multiplicative scale. For example, from a public health perspective, a positive departure from additivity of effects implies that the number of cases attributable to 2 hazards in combination is larger than the sum of the numbers of cases that would be caused by each hazard separately (3).

The relative excess risk due to interaction (RERI), also referred to as ''ICR'' (interaction contrast ratio), provides one useful metric of departure from additivity of effects on a relative risk scale (4, pp. 340–342). Hosmer and Lemeshow (5) described an approach to calculating RERI, along with the associated asymptotic 95% confidence interval, using the output obtained from fitting a logistic regression model. This approach is appealing as it utilizes the output from a standard exponential odds regression model. Hosmer and Lemeshow (5) acknowledged the limitations of their proposed Wald-type interval estimates. Assmann et al. (6) subsequently demonstrated that bootstrapping may give better coverage of the 95% confidence interval for the estimate of RERI than the method proposed by Hosmer and Lemeshow. Recently, Zou (7) proposed an alternative approach to derivation of confidence intervals for additive interactions via a method of variance estimates recovery, referred to as ''MOVER.'' Similar to the approach advocated by Hosmer and Lemeshow, the approach proposed by Zou utilizes the

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estimated variance and covariance of the estimated coefficients from a standard exponential odds regression model (6, 7).

This article describes how additive interactions of odds ratios for logistic or binomial regression models can be easily assessed using standard commercial software packages, such as SAS (8) and STATA (9). The RERI is shown to be identical to the product term in a linear odds ratio or linear relative risk model, and the confidence interval obtained via the method advocated by Hosmer and Lemeshow (5) is shown to be equivalent to the Wald-type confidence interval for this product term. Storer et al. (10) suggested that, when working with linear relative risk models, Wald-type statistics should be avoided entirely. They recommended the use of likelihood ratio or score statistics in these settings (10). Similarly, Greenland warned that, when working with linear relative risk models, Wald-type confidence intervals perform poorly at typical sample sizes; he argued for the use of confidence intervals based upon likelihood ratio or score statistics (11–13). Maldonado and Greenland (14) found, via simulation analyses, that the performance of Wald-type confidence intervals was poor when fitting nonmultiplicative models, while the likelihood ratio interval consistently performed well. We present a simple approach to deriving likelihood-based confidence intervals for RERI and illustrate how these bounds may differ from the asymptotic bounds used by previous authors (5, 7, 15).

MATERIALS AND METHODS

Let A and B denote 2 explanatory variables measured in an epidemiologic study. A logistic regression analysis conducted via an exponential odds model of the form, odds $= e^{(\beta_0+\beta_1 A+\beta_2 B)}$, implies that the effects of A and B are additive on an exponential scale.

A linear odds ratio model offers a useful alternative to the log-linear model when a researcher is interested in questions regarding departure from additivity of the effects of the exposures. The linear odds ratio model has the form, odds $= e^{(\beta_0)}(1 + \beta_1 A + \beta_2 B)$, where $\beta_1$and β_2 represent the excess odds ratio per unit of exposure to A and B, respectively. Under a linear odds ratio model, in the absence of a product interaction term between A and B, the effects of these 2 factors are assumed to affect the odds of disease in an additive fashion. A test of departure from additivity involves inclusion of a product interaction term leading to a model of the form, odds $= e^{(\beta_0)}(1 + \beta_1 A + \beta_2 B + \beta_3 AB)$.

Relative excess risk due to interaction

The RERI has become a widely used metric of departure from additivity of effects on a relative risk (RR) scale. For a pair of dichotomous exposure variables, A and B, Hosmer and Lemeshow (5) defined this quantity as $\mathrm{RR}(AB) - \mathrm{RR}(A\bar{B}) - \mathrm{RR}(\bar{A}B) + 1$. This could be written equivalently as the excess additive risk divided by the baseline risk (the risk among those exposed to neither A nor B). Following Hosmer and Lemeshow, we focus on the scenario in which the odds ratio approximates the relative risk. Consider rewriting the expression for RERI in terms of excess relative risk (ERR), where ERR = RR − 1, as follows:

$$\begin{aligned}\mathrm{RERI} &= [\mathrm{ERR}(AB)+1]-[\mathrm{ERR}(A\bar{B})+1]-[\mathrm{ERR}(\bar{A}B)+1]+1\\ &= \mathrm{ERR}(AB) - \mathrm{ERR}(A\bar{B}) - \mathrm{ERR}(\bar{A}B).\end{aligned}$$

In a linear odds ratio model of the form, odds $= e^{(\beta_0)}(1 + \beta_1 A + \beta_2 B + \beta_3 AB)$, the coefficient β_3 describes departure from additivity of the exposures effects on an odds ratio scale. Therefore, $\beta_3 = \mathrm{ERR}(AB) - \mathrm{ERR}(A\bar{B}) - \mathrm{ERR}(\bar{A}B)$, and β_3 may be taken as estimator of RERI (while $\beta_1$and β_2 may be taken as estimators of $\mathrm{ERR}(A\bar{B})$and $\mathrm{ERR}(\bar{A}B)$, respectively). Notably, if the effects of A and B are strictly additive on an odds ratio scale, $\beta_3 = 0$.

Likelihood-based confidence intervals for parameters in a linear odds ratio model are generally preferred over Wald-type confidence intervals as they have better coverage behavior (10–14). A likelihood-based confidence interval can be derived by comparing the residual deviance (i.e., −2 log-likelihood) of a model in which all parameters are allowed to vary to the residual deviance of a model in which a parameter of interest is fixed at a specified level while allowing the other model parameters to vary (1, pp. 229–230). The 2 values that fix the parameter of interest and result in a change in the residual deviance by $\chi^2_{(1,\alpha)}$ represent the $100(1 - \alpha)\%$ upper and lower confidence bounds for this parameter.

Fitting the linear odds ratio model

Methods for evaluation of measures of additive interaction within the context of standard exponential regression models might have been promoted on the premise that fitting the linear odds ratio model would require specialized software. However, the linear odds ratio model may be readily fitted using the SAS statistical package. PROC NLMIXED produces likelihood estimates that are based on adaptive Gaussian quadrature (8). A linear odds ratio model of the form, odds $= e^{(\beta_0)}(1 + \beta_1 A + \beta_2 B + \beta_3 AB)$, may be fitted via SAS as follows:

```
proc nlmixed data = ;
  odds=exp(b0)*(1+ b1*A + b2*B + b3*A*B);
  model outcome ~ binary(odds/(1+odds));
  run;
```

The term "`odds`" specifies that the odds of disease are the product of `exp(b0)` and the linear term "`(1+ b1*A + b2*B + b3*A*B)`." The model statement specifies that the events follow a binomial distribution with the probability, `P=(odds/(1+odds))`. The parameters `b0, b1, b2`, and `b3` are estimated from the data. A simple SAS macro can be used to obtain likelihood-based confidence bounds (Web Appendix 1). (This information is described in the first of 2 supplementary appendixes; each is referred to as "Web Appendix" in the text and is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) STATA code for fitting a linear odds ratio model and obtaining likelihood-based confidence bounds is provided as well (Web Appendix 2).

Bootstrapping

Bootstrapping offers another approach for deriving approximate confidence intervals for parameters derived via

Table 1. Distribution of Cases and Controls With Respect to Alcohol Use and Smoking in a Study of Oral Cancer Among 458 Veterans[a]

A = Alcohol Use	*B* = Smoking	Oral Cancer	
		Cases, no.	Controls, no.
1	1	225	166
1	0	6	12
0	1	8	18
0	0	3	20

[a] Data are from an example presented by Rothman and Keller (18) and Hosmer and Lemeshow (5).

Table 3. Distribution of Cases and Controls With Respect to Sports Participation and Smoking in a Case-Control Study of Herniated Lumbar Discs[a]

A = No sports	*B* = Smoking	Herniated Disc	
		Cases, no.	Controls, no.
1	1	36	28
1	0	31	20
0	1	138	113
0	0	82	126

[a] Data are from the study by Mundt et al. (19).

a linear relative risk model (16). Assmann et al. (6) proposed a nonparametric approach to bootstrapping of confidence intervals for RERI. They suggested that a number of bootstrap replications should be taken (with replacement) from the original sample, each replication being the same size as the original sample. The RERI is then estimated in each replication, and the 95% confidence interval for RERI is estimated as the 2.5th and 97.5th percentiles of the resulting distribution (6, 17).

Example 1

Consider the data examined by Hosmer and Lemeshow (5) to illustrate their approach to calculating confidence intervals for RERI. The data concern smoking and alcohol use in relation to oral cancer among male veterans under the age of 60 years (18). Hosmer and Lemeshow reported that, for the data shown in Table 1, RERI = 3.74, and the asymptotic 95% confidence interval for RERI was −1.85, 9.33. Zou (7) proposed an alternative method to deriving confidence intervals for RERI; the resultant 95% confidence interval obtained via Zou's method is −11.41, 21.84.

A linear odds ratio model of the form, $\text{odds} = e^{(\beta_0)}(1 + \beta_1\text{alcohol} + \beta_2\text{smoking} + \beta_3\text{alcohol} \times \text{smoking})$, was fitted to these data. Table 2 reports the parameter, estimate, standard errors, Wald-type 95% confidence bounds, and likelihood-based 95% confidence bounds. The value for $\hat{\beta}_3$ equals the estimate of RERI, and the Wald-type 95% confidence interval obtained via fitting the linear odds ratio model −1.85, 9.33 is equivalent to the asymptotic 95% confidence interval derived via Hosmer and Lemeshow's approach. The likelihood-based 95% confidence bounds for $\hat{\beta}_3$ are −3.29, 17.21.

A bootstrapped confidence interval was derived via 1,000 bootstrap replications of the original data. The 95% confidence interval $-10.77, 1.6 \times 10^7$ was wide as a consequence of sparse cells in some bootstrap simulations. The 5th and 95th centiles of the resulting bootstrap sampling distribution of RERI, which provide 90% confidence bounds via a bootstrap percentile method, were −1.50 and 19.59, which may be contrasted to the likelihood-based 90% confidence interval −1.34, 13.10. These results suggest that the nonparametric bootstrap approach proposed by Assmann et al. (6) does not perform well when applied to an analytical data structure of this size.

Table 2. Alcohol Use and Smoking in Relation to Oral Cancer in a Study of 458 Veterans[a,b,c]

Parameter	Estimate	Standard Error	Wald-Type 95% Bounds	Likelihood-based 95% Bounds
Constant	−1.90	0.62	−3.11, −0.68	−3.34, −0.83
Alcohol	2.33	2.65	−2.88, 7.55	−0.26, 17.21
Smoking	1.96	2.22	−2.41, 6.34	−0.27, 14.14
Alcohol × smoking	3.74	2.85	−1.85, 9.33	−3.29, 17.21

[a] Data are from an example presented by Rothman and Keller (18) and Hosmer and Lemeshow (5).

[b] Output was from fitting of a linear odds ratio model to the data in Table 1 of the present paper.

[c] Estimates were obtained via fitting of a model of the form: $\text{odds} = e^{(\beta_0)}(1 + \beta_1\text{alcohol} + \beta_2\text{smoking} + \beta_3\text{alcohol} \times \text{smoking})$.

Example 2

Consider the data examined by Assmann et al. (6) to illustrate bootstrapping of confidence intervals for RERI. The data are derived from a case-control study of herniated lumbar disc in relation to sports participation and smoking (19) (Table 3). As in Assmann et al. for the purposes of this example, we ignore the matched design. The estimate of RERI is −1.28 (Table 4). Using the approach described by Hosmer and Lemeshow (5), we found that the associated 95% confidence interval is −3.12, 0.56; while using the approach described by Zou, the associated 95% confidence

Table 4. Sports Participation and Smoking in Relation to Herniated Lumbar Discs[a,b]

Parameter	Estimate	Standard Error	Wald-Type 95% Bounds	Likelihood-based 95% Bounds
Constant	−0.43	0.14	−0.71, −0.15	−0.71, −0.15
No sports	1.38	0.76	−0.12, 2.88	0.28, 3.52
Smoking	0.88	0.36	0.18, 1.58	0.29, 1.73
No sports × smoking	−1.28	0.94	−3.12, 0.56	−3.62, 0.43

[a] Data are from the study by Mundt et al. (19).

[b] Output was from fitting of a linear odds ratio model to the data in Table 3 of the present paper.

interval is −3.66, 0.42. Direct fitting of a linear odds ratio model with a product term describing departure from additivity of effect on the odds ratio scale results in a likelihood-based 95% confidence interval of −3.62, 0.43. Bootstrapping 1,000 replications of the original data results in a 95% confidence interval for RERI of −3.63, 0.53.

RESULTS AND DISCUSSION

This article illustrates how to directly evaluate additive interactions on the odds ratio scale within the context of a linear odds ratio regression model. An assessment of departure from additivity of effects on an odds ratio scale is encompassed within a regression analysis context, with a parameter representing RERI estimated simultaneously with all other regression model parameters. A formal statistical test of the contribution of a product term describing departure from additivity of effects is obtained by contrasting nested models. Although significance testing shouldn't be the sole criterion for evaluation of odds ratio modification (on a multiplicative or additive scale), such a test statistic provides a useful piece of information in assessment of statistical interactions.

A number of authors have cautioned against the use of Wald-type confidence intervals for nonmultiplicative models (11, 14, 20). In general, relative risk models, such as the linear odds ratio model, and likelihood-based confidence intervals are preferred because methods based on asymptotic variance estimates may be misleading (11). The approach to deriving confidence intervals for RERI recommended by Hosmer and Lemeshow and the approach subsequently advocated by Zou utilize the estimated standard errors of coefficient estimates. The first example in this paper illustrated the difference between likelihood-based 95% confidence intervals for RERI and the asymptotic 95% confidence intervals used by previous authors (in analyses of the same data). The second example illustrated that, in a larger study, the confidence intervals derived via these various approaches tend to be more similar, although the likelihood-based confidence bounds are still preferred and are readily used for these purposes.

An alternative to deriving likelihood-based confidence intervals for RERI is to bootstrap confidence intervals, as suggested by Assmann et al. (6). However, this approach has its limitations. For exponential models, the bootstrap can be thought of as 1 way of constructing the likelihood intervals; for nonmultiplicative models, DiCiccio and Efron (16) caution that, although likelihood-based intervals are accurate in a conditional sense, in order to get good conditional properties bootstrap sampling would have to be done according to the appropriate conditional distribution, which is usually difficult to implement. Barlow and Shun (20) found that, in the simulation scenarios that they considered, bootstrapped confidence intervals did not perform well for linear relative risk models, while likelihood-based confidence intervals had values close to nominal coverage. Furthermore, as we observed in example 1, the bootstrapping approach proposed by Assmann et al. (6) may perform poorly for small tabulations of data if samples are too small to rely upon (21).

Following Hosmer and Lemeshow, we focus on the fitting of regression models that estimate the odds ratio. Linear relative risk models of the form, $\text{risk} = e^{(\beta_0)}(1 + \beta_1 d)$, may be of interest in some settings (e.g., analyses of incidence proportions in closed cohorts); further, it has been noted that for common outcomes RERI is preferably calculated in terms of risk ratios rather than odds ratios (7). SAS PROC NLMIXED is highly flexible, and an analogous approach to fitting a linear relative risk model is possible to implement as well.

Importantly, these models do not address questions regarding interactions that influence the distribution of times to disease onset (e.g., whether the empirical induction period among those exposed to A differs in the presence of B). Nor do these methods consider scenarios in which the temporal ordering of exposures impacts their joint effects, as might be envisioned under a multistage model for a disease process. While these are important questions, alternative methods of analysis are necessary to investigate them (22–24).

Greenland (12) noted that an evaluation of departure from additivity of relative risks, as explored herein, is not equivalent to an evaluation of departure from additivity of effects on the risk scale (except in the special case where there is a single stratum of data defined by covariates). In an additive risk model, departure from additivity is defined by the quantity, $R(AB) - R(A\bar{B}) - R(\bar{A}B) - R(\bar{A}\bar{B})$, and therefore depends upon the baseline risk estimate, $R(\bar{A}\bar{B})$, which may vary across strata of covariates and is often not readily estimable in case-control analyses. In contrast, we have focused on departures from additivity of relative risks and specifically on a quantity, RERI, which does not depend upon $R(\bar{A}\bar{B})$ and is estimable in both cohort and case-control designs. Along lines similar to those of Greenland (12), Skrondal (25) noted that, if the population model of the exposure-disease association conforms to an additive risk model, then RERI will vary across the strata of covariates; correct model specification, not surprisingly, is a fundamental requirement for valid estimation of interaction terms.

Concepts of interaction play an important role in epidemiologic data analysis and interpretation. This paper illustrates an approach to estimation of interaction on an additive scale within a multiple logistic regression framework, along with derivation of appropriate likelihood-based confidence intervals for this metric. Procedures for deriving confidence intervals based upon likelihood ratio statistics have long been advocated as the preferred method for parameters in linear relative risk models (11–13). The approach presented here should facilitate assessment of additive interaction on an odds ratio scale.

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