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# Confidence intervals for the interaction contrast ratio: A simple solution with SAS PROC NLMIXED and SAS PROC NLP

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The interaction contrast ratio (ICR[1]), formerly called relative excess risk due to interaction (RERI), is a well established quantitative measure for interaction in epidemiological studies. Estimates for the ICR can be easily derived from an ordinary logistic regression model with an interaction term. However, calculation of confidence intervals is complicated by the fact that the ICR is a non-linear combination of the parameters from this model. As such, bootstrapping or the multivariate delta method must be used for computation of confidence intervals. Software code to this problem has been offered in this journal[2], but also at other instances[3-5]. However, these codes are still rather lengthy and somewhat difficult to use. We show here that fitting the original model with SAS PROC NLMIXED or SAS PROC NLP allows simple solutions to this problem.

For illustration we use an example on the association of sun protection, iris color, and uveal melanoma from a case-control study recently reported by two of the authors[6]. Actually, this example initiated our research reported here, as the SAS code by Lundberg[2] did not give confidence intervals for the ICR. The SAS code 1 in the Supplemental Digital Content (SDC) 1 gives the data set and PROC LOGISTIC code for fitting the ordinary logistic regression model. Proceeding like this, we now might use the published Lundberg code to compute the ICR and its corresponding confidence interval. We propose instead to fit the standard logistic regression with PROC NLMIXED using code 2 in SDC 1. This involves, as compared to PROC LOGISTIC, some small additional effort as we are forced to write down explicitly the parameters to be estimated and the model equation. However, this effort is more than compensated with the opportunity of calculating functions of model parameters via the ESTIMATE statement, where these functions do not have to be linear. As such, the additional ESTIMATE statement codes the standard formula[7] for the ICR.

PROC NLMIXED calculates confidence intervals for these additional estimates via the multivariate delta method. From the NLMIXED code we find an estimated ICR of 0.636 with a 95%-confidence interval of [-0.234, 1.506].

As a limitation of this first proposal we note that PROC NLMIXED only computes Wald confidence intervals (or such that use the t distribution). Zou[4] showed that these rely on the assumption of symmetric confidence intervals for risk ratios, and Richardson and Kaufman[5] argue that likelihood-based confidence intervals should be used instead. To cope with this, PROC NLP from the SAS/OR module can be used, as this procedure allows the computation of profile likelihood (PL) confidence intervals. Unfortunately, PROC NLP does not allow estimating non-linear combinations of parameter estimates and we are forced to reparametrize the model such that the ICR (for which we like to have PL confidence intervals) becomes an original model parameter. Straightforward calculation yields:

$$b_{interaction} = \ln\left(\frac{ICR + \exp(b_{protect}) + \exp(b_{iriscolor}) - 1}{\exp(b_{protect})\exp(b_{iriscolor})}\right). \qquad (1)$$

The reparametrized model can be fitted via PROC NLP with code 3 in SDC 1. Submitting this code, we again find an estimated ICR of 0.636, this time with a 95%-confidence interval of [-0.365, 1.529]. As compared to the Wald interval, both PL interval bounds are larger in absolute values where this difference is larger for the lower bound.

In summary, we proposed two methods for computing confidence intervals for the ICR in SAS that we feel are simpler and more robust (at least, in our case) as previously proposed methods. Of course, the ideas reported here could also be used to compute Wald and PL confidence intervals for the two other commonly used

measures of interaction, the attributable proportion due to interaction (AP) and the synergy index (S).

Legend of Supplemental Digital Content 1:

SAS code for calculating confidence intervals for the interaction contrast ratio with SAS PROC NLMIXED and SAS PROC NLP.

Reference List

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