



Invited Commentary

Invited Commentary: Some Advantages of the Relative Excess Risk due to Interaction (RERI)—Towards Better Estimators of Additive Interaction

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In the accompanying commentary, Rose and van der Laan (*Am J Epidemiol.* 0000;000(00):000–000) criticize the relative excess risk due to interaction (RERI) measure, the use of additive interaction, and the weighting approach we developed to assess RERI with case-control data. In this commentary, we note some of the advantages of using additive measures of interaction, such as RERI, in making decisions about targeting interventions toward certain subgroups and in assessing mechanistic interaction. We discuss the relationship between Rose and van der Laan's estimator for case-control data and the one we had previously proposed. We also develop a new doubly robust estimator for determining the RERI with case-control data when the prevalence or incidence of the outcome is known.

additive interaction; case-control studies; doubly robust estimator; subgroup analysis; synergism

Abbreviation: RERI, relative excess risk due to interaction.

We thank Rose and van der Laan (1) for their interesting contribution to the literature. We believe the field would benefit from further methodological development oriented towards improving the precision of estimates and reducing dependence upon modeling assumptions. We look forward also to the promised further extensions of the approach of Rose and van der Laan to the setting of interaction parameters.

Rose and van der Laan comment on our recent paper (2), in which we developed a weighting approach to estimate additive interaction parameters from unmatched case-control data. Our approach estimates a marginal relative excess risk due to interaction (RERI) parameter (3) for the underlying population base, under a rare-outcome assumption. Estimating RERI is desirable from a public health perspective because it allows an investigator to assess whether it would be preferable to target an intervention toward certain subgroups if resources are limited (4–6). Moreover, estimating RERI is desirable because it allows one to easily assess whether mechanistic interaction may be present in a sufficient-cause sense (6–9): Provided that the effects of both exposures are unconfounded, $RERI > 0$ implies a sufficient-cause interaction under the monotonicity assumption that the effects of the exposures are never preventive for any individual (5, 8);

$RERI > 1$ implies a sufficient-cause interaction without requiring this monotonicity assumption (6, 8).

The approach we developed was designed to counter arguments against the use of RERI, the so-called “uniqueness” problem and “misspecification” problem (10). We showed that by using our weighting approach, both supposed problems vanish (2, 11). The marginal RERI that our approach estimated was unique and would give a single value of additive interaction in settings that include, but are not limited to, those in which the true underlying outcome model is additive; moreover, our approach did not require correct specification of an outcome model (only correct specification of models for the weights). As noted above, RERI also has the advantage that there are simple conditions for RERI (with or without monotonicity assumptions) to evaluate evidence for mechanistic sufficient-cause interaction (6, 8, 9). Such simple conditions are generally not available for other measures of additive interaction from case-control data (3, 10). In addition, our weighting approach places fewer restrictions upon the sufficient-cause model than do other approaches to estimating RERI (2, 12).

Rose and van der Laan (1) offer some critiques of the approach we developed. They comment that it would be

desirable to have a more efficient estimator. We agree and would welcome such a development for additive interaction, though they do not offer one in their paper. In their comments on efficiency, Rose and van der Laan also argue that targeted maximum likelihood estimators are themselves efficient. While we agree that certain efficiency properties can be ascribed to this approach, we note in the Web Appendix (available at <http://aje.oxfordjournals.org/>) that the efficiency properties of case-control-weighted targeted maximum likelihood estimators are subtle and that even when a correct model for the outcome is used, these may not in fact be guaranteed to improve upon the weighting approach. Rose and van der Laan also suggest that the parameter of interest should not depend on the study design. We only partially agree. Study designs in some cases dictate what can be estimated. Often an investigator must be content with choosing between a parameter that can be estimated from the design or abandoning the study and the question of interest entirely. While additive interaction using absolute risks would certainly be preferable to RERI, it is not generally possible to estimate additive interaction for risks with many case-control designs.

Rose and van der Laan also critique our rare-outcome assumption. Within the context considered in our paper, this critique seems less reasonable. Our approach was developed to estimate RERI with case-control data. In many case-control studies, the case-control design is selected because the outcome is rare. The rare-outcome assumption will then generally be quite reasonable in numerous cases-control designs. Moreover, our weighting approach will also be applicable without the rare-outcome assumption in many contemporary case-control designs when incidence density sampling is used such that the “controls” are sampled from the population rather than only from the noncases (13). Furthermore, Rose and van der Laan only circumvent the rare-outcome assumption (an evasion that is often not needed in case-control studies) by requiring knowledge of the population prevalence of the outcome, a quantity that is sometimes available (as in nested case-control designs) but often is not. Rose and van der Laan thus trade off an assumption that is often reasonable—that of a rare outcome—with one that is generally less reasonable—that the prevalence of the outcome in the study population is known. This, in our view, is not a good trade.

We certainly do not believe that our weighting approach provides an ideal estimator. In fact, in most cases, we believe our weighting estimator will be inferior, at least on efficiency grounds, to delta-method-based approaches to RERI using logistic regression (6, 14). Again, the weighting approach we developed was intended primarily to counter objections to the use of RERI, the so-called “uniqueness” and “misspecification” problems (10). Ideally, an approach to RERI could be developed that 1) was doubly robust, 2) was efficient, and 3) did not require external knowledge of the prevalence of the outcome. We have developed such an approach for cohort data (15). We have struggled with a similar approach for case-control data; we have obtained an estimator for RERI that is doubly robust and more efficient than the weighting approach but still requires external knowledge of the prevalence of the outcome (see Web Appendix), though the dependence on the

prevalence is relatively weak. We would welcome further developments along the lines of Rose and van der Laan’s suggestions that accomplished the 3 goals noted above. We believe that the field may get there eventually, but we are not there yet.

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