R Function for Additive Interaction Measures

To the Editor:

Interaction analyses are commonplace in the epidemiology literature. Predominantly, investigators assess for interaction on the multiplicative scale when the outcome of interest is binary.[1] For example, the standard exponentiated logistic regression coefficient corresponding to the product of two exposures represents the multiplicative ratio by which the joint effect (on the relative risk or odds ratio scale) of both exposures exceeds their individual contributions. Yet multiplicative measures alone are insufficient to fully assess the public health relevance of exposure interactions. For example, they can mislead strategies to target interventions to subgroups, thus reducing net benefit in the population.[2]

To overcome these limitations, several measures of interaction on the additive scale have been proposed,[3,4] and editorial policy for the journal *Epidemiology* advocates their reporting as common practice. Additive measures assess the difference, rather than the ratio, by which the joint effect exceeds the individual contributions by the two exposures; common examples for a binary outcome and binary exposures appear in the Table (rows 1–3).

Such measures accurately identify subgroups to which interventions should be targeted[2] and, furthermore, can be used to assess for "mechanistic interactions" based on the sufficient cause framework.[5] Examples of mechanistic interactions include sufficient cause synergism and compositional epistasis (Table, rows 4–5). Under the assumption that there is no unmeasured confounding of either exposure–outcome relationship, a true relative excess risk due to interaction surpassing specific thresholds is sufficient to guarantee the existence of synergism and compositional epistasis. These thresholds on the relative excess risk due to interaction can be relaxed if one or both of the exposures can be assumed to have monotonic effects; that is, if the direction of the exposure's causal effect would be the same direction for all individuals in the population.[5]

Existing software for additive interaction analyses in SAS and STATA[6] allows the user to compute these measures, including the proportion of the effects attributable to interaction,[5,6] along with confidence intervals. The present software provides a similar implementation in R with more options and flexibility than other R implementations, and it does not require recoding of exposures. It also more directly

Table. Additive and Mechanistic Interactions Implemented in R Function

	Definition	Interpretation	Assumptions
Additive interactions			
RERI (relative excess risk due to interaction)	$RR_{11} - RR_{01} - RR_{10} + 1$	Difference between the joint RR and the separate contributions by the two exposures	None when interpreted associationally; otherwise, NUCA for one or both exposures
Attributable proportion	$\frac{RERI}{RR_{11}}$	Proportion of outcome risk in the doubly exposed group attributable to interaction	None when interpreted associationally; otherwise, NUCA for one or both exposures
Proportion of joint effect due to interaction	$\frac{RERI}{RR_{11}-1}$	Proportion of the joint effects that is attributable to interaction	None when interpreted associationally; otherwise, NUCA for one or both exposures
Mechanistic interactions			
Synergy	There exists an individual with $D_{11} = 1$ but $D_{01} = D_{10} = 0$.	Presence of a mechanism such that some individuals would experience the outcome under both exposures, but not under either exposure alone	NUCA; optionally monotonicity assumptions for less stringent tests
Compositional epistasis	There exists an individual with $D_{11} = 1$ but $D_{01} = D_{10} = D_{00} = 0$.	Presence of a mechanism such that some individuals would experience the outcome if and only if both exposures were present	NUCA; optionally monotonicity assumptions for less stringent tests
Other measures			
Proportion of joint effect due to exposure 1	$\frac{RR_{10}}{RR_{11}-1}$	—	None when interpreted associationally; otherwise, NUCA for one or both exposures
Proportion of joint effect due to exposure 2	$\frac{RR_{01}}{RR_{11}-1}$	—	None when interpreted associationally; otherwise, NUCA for one or both exposures

RERI indicates relative excess risk due to interaction; D, binary outcome variable; E_1 and E_2, binary exposure variables; NUCA, no-unmeasured-confounding assumptions for one or both exposure–outcome relationships.[5] $RR_{ab} = \frac{P(D=1|E_1=a,\ E_2=b)}{P(D=1|E_1=0,\ E_2=0)}$, where $a, b \in \{0,1\}$, which can be replaced with an odds ratio as appropriate to study design. D_{ab} = potential outcome for D under an intervention setting $E_1 = a$ and $E_2 = b$.

The authors declare that they have no conflicts of interest.

M.M. was supported by National Defense Science & Engineering Graduate Fellowship 32 CFR 168a. T.V.W. was supported by National Institutes of Health grant R56 ES017876.

ISSN: 1044-3983/18/2901-00e5
DOI: 10.1097/EDE.0000000000000752

allows for the assessment of mechanistic interaction. The user-friendly R function *additive_interactions* addresses all these topics. The code is publicly available (https://osf.io/7ccpp/), along with documentation and usage examples. We briefly describe the functionality here.

The user passes a standard model object from a logistic regression (fit via R's *glm*) of the outcome on both binary exposures and their interaction. The linear predictor can include confounders of arbitrary specification. Using fitted coefficients and their estimated variance–covariance matrix, the function computes estimates of the measures listed in the Table along with confidence intervals and *P* values based on the delta method.[5] To test for mechanistic interactions, *additive_interactions* allows the user specify whether zero, one, or two of the exposures are assumed to have monotonic effects. Appropriate hypothesis tests are then conducted for both sufficient–cause interaction and compositional epistasis. All output is returned in the form of a dataframe. In the online documentation, we demonstrate application of the function to simulated data.

Additive interaction measures are typically conceptualized for settings in which both exposures are positively associated with the outcome ($RR_{10} > 1$ and $RR_{01} > 1$, denoting the joint relative risk $RR_{ab} = \frac{P(D=1|E_1=a,\ E_2=b)}{P(D=1|E_1=0,\ E_2=0)}$, where $a, b \in \{0,1\}$). Our function *additive_interactions* handles other cases by giving the option of automatically recoding of one or both exposures against new reference levels defined by the joint category with the lowest overall risk.[7]

We hope that the availability of a general, user-friendly R function may reduce a potential barrier to widespread reporting of additive interaction measures.

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Pandemic Influenza A H1N1 Vaccination and Subsequent Risk of Type 1 Diabetes in Norway

To the Editor:

Given the association between the 2009 pandemic influenza A H1N1 vaccination and narcolepsy,[1] it is of interest to study other human leukocyte antigen (HLA)–associated autoimmune diseases such as type 1 diabetes. While an analysis from Stockholm did not show any association with type 1 diabetes (hazard ratio [HR] = 1.0; 95% CI = 0.7, 1.5),[2] a Swedish nationwide analysis showed an increased incidence of type 1 diabetes (HR = 1.23; 95% CI = 1.00, 1.51 in 10- to 19-year-olds; HR = 1.13, 95% CI = 1.00, 1.29 in all <30 years of age),[3] which has raised concerns that warrant further study.[4] Because type 1 diabetes develops over several months or years,[5] a longer follow-up is important. During the 2009–2010 influenza pandemic in Norway, the whole population was offered an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine (Pandemrix) free of charge or with a small administration fee.[6] Using nationwide data from Norway, we investigated whether Pandemrix vaccination in 2009–2010 was associated with increased risk of subsequent type 1 diabetes from 2009 to 2014.

We included all residents in the Norwegian National Registry ages 30 years and younger per 1 October 2009. Dates of vaccination were obtained from the Norwegian Immunization Register, in which Pandemrix registration was mandatory. We identified newly onset type 1 diabetes during the period 1 October 2009 to 30 June 2014 from combining information on antidiabetic drugs dispensed from pharmacies in Norway from the Norwegian Prescription Database, specialist care diagnosis, from the Norwegian Patient Registry and primary care diagnoses from the reimbursement database (eFigure 1; http://links.lww.com/EDE/B264). These nationwide databases are independently reported and mandatory with a high level of completeness.

Information from the different sources was linked using the personal identification number assigned to all residents in Norway. Further details of

All authors have completed and submitted the ICMJE form for Disclosure of Potential Conflicts of Interest. No disclosures were reported.
This research was partly supported by the Norwegian Institute of Public Health and a grant from the Norwegian Health South East Authority.
Data sharing: No additional data included. Data used in this study are available from the included registers with approval from the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Authority. Code for replication can be requested.
SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

ISSN: 1044-3983/2017/2901-00e6
DOI: 10.1097/EDE.0000000000000748