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Attributing effects to interactions

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Abstract

A framework is presented that allows an investigator to estimate the portion of the effect of one exposure that is attributable to an interaction with a second exposure. We show that when the two exposures are independent, the total effect of one exposure can be decomposed into a conditional effect of that exposure and a component due to interaction. The decomposition applies on difference or ratio scales. We discuss how the components can be estimated using standard regression models, and how these components can be used to evaluate the proportion of the total effect of the primary exposure attributable to the interaction with the second exposure. In the setting in which one of the exposures affects the other, so that the two are no longer independent, alternative decompositions are discussed. The various decompositions are illustrated with an example in genetic epidemiology. If it is not possible to intervene on the primary exposure of interest, the methods described in this paper can help investigators to identify other variables that, if intervened upon, would eliminate the largest proportion of the effect of the primary exposure.

In some settings, the effect of a particular exposure may be substantially altered in the presence or absence of a second exposure, so that some form of interaction exists between these two exposures.[1,2] In such cases, it may be of interest to determine the extent to which the overall effect of the primary exposure of interest is due to the presence of the secondary exposure, and the primary exposure's interaction with it. We present an analytic framework within which to address such questions. We show that, if the distributions of the two exposures are statistically independent in the population, then the overall effect of the primary exposure can be decomposed into two components - the first being the effect of the primary exposure when the secondary exposure is removed, and the second being a component due to interaction. Such decompositions can be useful in settings in which it is not possible to intervene on the primary exposure of interest and an investigator is interested in trying to identify other variables that, if intervened upon, would eliminate much or most of the effect of the primary exposure of interest. We show how this decomposition applies on an additive scale and on a risk ratio scale, and how regression models can be used to estimate each of the components. We discuss extensions to settings in which the two

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exposures are not independent but rather when one affects the other, and we also discuss a decomposition of joint effects of both exposures and relate these to Rothman's measures of the attributable proportion due to interaction.[1–3] The decompositions are illustrated with an example from genetic epidemiology. We begin with introducing notation. We will keep both the notation and the setting relatively simple in the paper but consider more complex settings in the Appendix and eAppendix.

Definitions and Notation

We will let G and E denote two exposures of interest. These may be genetic and environmental exposures, respectively, but they could also both be genetic, or both environmental, or one or both could be behavioral. We will, for simplicity in exposition, refer to the first as a genetic exposure and the second as an environmental exposure. When the ordering of the exposures is relevant we will assume that G precedes E. We will assume for simplicity that both exposures are binary; however we consider more general settings in the appendix.

Let Y be an outcome of interest that may be binary or continuous. When the outcome is binary, for variable(s) X, we will use $p_x = P(Y = 1|X = x)$ to denote the probability of the outcome conditional on $X = x$. If the effect of G on Y is unconfounded, then $p_{g=1} - p_{g=0} = P(Y = 1|G = 1) - P(Y = 1|G = 0)$ would equal to the effect of G on Y. If the effect of E on Y is unconfounded, then $p_{e=1} - p_{e=0} = P(Y = 1|E = 1) - P(Y = 1|E = 0)$ would equal to the effect of E on Y. In the exposition in the text, we will assume that there is no confounding for the effects of G and E on Y, but in the appendix we consider analogous results when the effects are unconfounded only conditional on some set of covariates C.

With a binary outcome we will also use $p_{ge} = P(Y = 1|G = g, E = e)$ to denote the probability of the outcome when $G = g$ and $E = e$. The standard interaction contrast on the additive scale would be written as $(p_{11} - p_{10} - p_{01} + p_{00})$ and assesses the extent to which the effect of both exposures together exceeds the effect of each considered separately.

Attributing Total Effects to Interactions Under Independence

Suppose now that the two exposures G and E are statistically independent (and thus uncorrelated) in the population and suppose that the effects of G and E on Y are unconfounded. We show in the Appendix that:

$$(p_{e=1} - p_{e=0}) = (p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})P(G=1).$$

We can decompose the overall effect of E on Y into two pieces. The first piece is the conditional effect of E on Y when $G = 0$; the second piece is the standard additive interaction, $(p_{11} - p_{10} - p_{01} + p_{00})$, multiplied by the prevalence of $G = 1$. We can then attribute the total effect of E on Y to the part that would be present still if G were 0 (this is $p_{01} - p_{00}$), and to a part that has to do with the interaction between G and E (this is $(p_{11} - p_{10} - p_{01} + p_{00})P(G = 1)$). If we could set the genetic exposure to 0, we would remove the part that is due to the interaction and would be left with only $p_{01} - p_{00}$.

Since we can do this decomposition, we might de.ne a quantity $pAI_{G=0}(E)$ as the proportion of the overall effect of E that is attributable to interaction, with a reference category for the genetic exposure of $G = 0$, as

$$pAI_{G=0}(E)=\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(G=1)}{(p_{e=1}-p_{e=0})}.$$

The remaining portion $(p_{01} - p_{00})/(p_{e=1} - p_{e=0})$ is the proportion of the effect of E that would remain if G were fixed to 0. The proportion attributable to interaction could then be interpreted as the proportion of the effect of E we would eliminate if we fixed G to 0.

If Y is continuous, again assuming that G and E are independent, we have a similar decomposition, $\mathbb{E}[Y|E = 1] - \mathbb{E}[Y|E = 0] =$

$$\mathbb{E}[Y|G=0,E=1]-\mathbb{E}[Y|G=0,E=0]+\{\mathbb{E}[Y|G=1,E=1]-\mathbb{E}[Y|G=1,E=0]-\mathbb{E}[Y|G=0,E=1]+\mathbb{E}[Y|G=0,E=0]\}P(G=1)$$

and we could likewise define the proportion attributable to interaction by

$$pAI_{G=0}(E)=\frac{\{\mathbb{E}[Y|G=1,E=1]-\mathbb{E}[Y|G=1,E=0]-\mathbb{E}[Y|G=0,E=1]+\mathbb{E}[Y|G=0,E=0]\}P(G=1)}{\mathbb{E}[Y|E=1]-\mathbb{E}[Y|E=0]}$$

The two components of the decomposition - the portion due to interaction and the portion due to the effect of E when G is fixed to 0 - also have an intuitive form within a regression framework.

Consider the following regression model in which Y might be binary or continuous:

$$\mathbb{E}[Y|G=g,E=e]=\alpha_0+\alpha_1 g+\alpha_2 e+\alpha_3 eg. \quad (1)$$

We show in the appendix that irrespective of whether the outcome is binary or continuous, if G and E are independent, then the total effect of E on Y is given by $\alpha_2 + \alpha_3 P(G = 1)$, the portion due to interaction is equal to $\alpha_3 P(G = 1)$, and the portion due to the effect when G is fixed to 0 is equal to α_2. Thus the proportion due to interaction is simply

$$pAI_{G=0}(E)=\frac{\alpha_3 P(G=1)}{\alpha_2+\alpha_3 P(G=1)}.$$

The portion due to the effect when G is fixed to 0 is simply the main effect of E in the regression model, α_2. The portion due to interaction is just the product coefficient α_3 multiplied by the probability that $G = 1$.

Note that under the assumption that G and E are independent, the roles of G and E can be interchanged. Thus with a binary outcome we could likewise decompose the total effect of G

on Y by: $(p_{g=1} - p_{g=0}) = (p_{10} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})P(E = 1)$. We could de.ne the proportion of the effect of G that is attributable to interaction (with a reference category for E of $E = 0$) as $pAI_{E=0}(G)=\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(E=1)}{(p_{g=1}-p_{g=0})}$. Expressed in terms of the coefficients of the regression model in (1) we have $pAI_{E=0}(G)=\frac{\alpha_3 P(E=1)}{\alpha_1+\alpha_3 P(E=1)}$.

To the best of our knowledge, this approach has not been previously described. The approach we have been considering thus far has assumed that the two exposures G and E are independent. As we will see later in the paper, the decomposition becomes somewhat more complicated when G and E are no longer independent in the population. Even under independence, the implications of the approach are also sometimes more subtle than they first appear. From the formulae above, the proportion attributable to interaction depends on the main effect coefficient for the primary exposure of interest, the interaction coefficient, and the prevalence of the secondary exposure. Because of this, it would, for example, be possible for the main effect of G, namely α_1, to be larger than the main effect of E, α_2, while it still also being the case that the proportion of the effect of G attributable to the interaction is larger than the proportion of the effect o E attributable to interaction. This could occur, for instance, if the prevalence of G was relatively small with the prevalence of E being comparatively larger.

Attributing Total Effects to Interactions on the Ratio Scale

Often, when an outcome is binary, a ratio scale is used to measure effects. We would define the relative risk for G as $RR_{g=1}=\frac{p_{g=1}}{p_{g=0}}=\frac{P(Y=1|G=1)}{P(Y=1|G=0)}$. Likewise we would de.ne the relative risk for E by $RR_{e=1}=\frac{p_{e=1}}{p_{e=0}}=\frac{P(Y=1|E=1)}{P(Y=1|E=0)}$. We can also define relative risks when G and E are considered together; we would de.ne the relative risk for the outcome Y, comparing $G = g$, $E = e$ to the reference category $G = 0$, $E = 0$, as

$$RR_{ge}=\frac{p_{ge}}{p_{00}}=\frac{P(Y=1|G=g,E=e)}{P(Y=1|G=0,E=0)}.$$

It is shown in the Appendix that if G and E are independent then we have the decomposition of the excess relative risk for E as:

$$(RR_{e=1}-1)=\kappa(RR_{01}-1)+\kappa(RR_{11}-RR_{10}-RR_{01}+1)P(G=1).$$

where κ is a scaling factor given by $\kappa=\frac{p_{00}}{p_{e=0}}$. As on the difference scale, so also on the ratio scale, we can decompose the excess relative risk for E, into two components: the first component is the excess relative risk for E if G were fixed to 0, $(RR_{01} - 1)$, and the second component is a portion of the effect due to interaction, $(RR_{11} - RR_{10} - RR_{01} + 1)P(G = 1)$. The contrast, $RR_{11} - RR_{10} - RR_{01} + 1$, is sometimes referred to as the "relative excess risk due to interaction" (RERI)[3] or the "interaction contrast ratio".[2] We can thus re-express the decomposition above as: $(RR_{e=1} - 1) = \kappa(RR_{01} - 1) + \kappa(RERI)P(G = 1)$. Because of the scaling factor κ, it does not necessarily make sense to estimate the specific portions, $\kappa(RR_{01} - 1)$, and $\kappa(RERI)P(G = 1)$, of the total effect, but if we consider the proportion of the effect of E attributable to interaction, then the scaling factor κ drops out and we obtain:

$$pAI_{G=0}(E) = \frac{(RERI)P(G=1)}{(RR_{01}-1)+(RERI)P(G=1)}.$$

By symmetry a similar decomposition holds for the overall effect of G on Y on the risk ratio scale and we have the proportion of the effect of G attributable to interaction as

$$pAI_{E=0}(G) = \frac{(RERI)P(E=1)}{(RR_{10}-1)+(RERI)P(E=1)}.$$

Often a logistic regression model is used in analyzing data with a binary outcome on the ratio scale. Consider the logistic regression model

$$logit\{P(Y=1|G=g,E=e)\}=\gamma_0+\gamma_1 g+\gamma_2 e+\gamma_3 eg. \quad (2)$$

If the outcome is rare, then odds ratios approximate risk ratios and $RERI$ is given approximately by $RERI \approx e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2} + 1$, and RR_{10} and RR_{01} can be estimated approximately by $RR_{10} \approx e^{\gamma_1}$ and $RR_{01} \approx e^{\gamma_2}$. We can thus still estimate all of the components of the proportions attributable to interaction using the estimates from the logistic regression in (2) and could compute these proportions by:

$$pAI_{G=0}(E) \approx \frac{(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(G=1)}{(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(G=1)}$$
$$pAI_{E=0}(G) \approx \frac{(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(E=1)}{(e^{\gamma_1}-1)+(e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2}+1)P(E=1)}.$$

As discussed in the Appendix, these same expressions can be used even when control is made for covariates in the logistic regression. This approach also works when using logistic regression in a case-control study. If the outcome is rare or incidence density sampling is used then we can estimate the various components in the decomposition by $RR_{10} \approx e^{\gamma_1}$, $RR_{01} \approx e^{\gamma_2}$, and $RERI \approx e^{\gamma_1+\gamma_2+\gamma_3} - e^{\gamma_1} - e^{\gamma_2} + 1$ and, in addition, $P(G = 1)$ and $P(E = 1)$ can be estimated approximately in a case-control study using the probability of G and E respectively among the controls. Thus we can proceed with estimating the components of the decomposition, even in a case-control study.

Standard errors for these various expressions, using the delta method, along with SAS and Stata code to estimate proportions attributable to interaction and their standard errors, using logistic regression, are given in the eAppendix. If the sample size is relatively small it may be preferable to use bootstrapping to obtain standard errors. A similar approach can also be employed if control is made for some set of covariates C or if one or both of the exposures are continuous rather than binary; see eAppendix for details.

One of the motivations often given for studying interaction, specifically on the additive scale, is to identify which subgroups would benefit most from intervention when resources are limited.[1–3] In settings in which it is not possible to intervene directly on the primary exposure of interest, one might instead be interested in which other covariates could be intervened upon to eliminate much or most of the effect of the primary exposure of interest. The methods here for attributing effects to interactions can be useful in assessing this and identifying the most relevant covariates for intervention.

Relaxing the Independence Assumption

Our discussion up until now has assumed that the distributions of the two exposures are statistically independent in the population. This assumption may not always be plausible. If *G* and *E* represent genetic and environmental exposures, then the assumption of independence in the population is often not unreasonable, though there are documented cases[4, 5] in which genetic variants do affect environmental exposures and so the assumption has to be assessed on a case-by-case basis. When the exposures are two environmental factors, or two behavioral factors, the two exposures may often be correlated with each other. In this section we will consider what can be concluded when the two exposures are instead correlated.

We will assume here that the ordering of the two exposures is known (e.g. that *G* precedes *E*). In this setting, even if *G* affects *E*, the decompositions we have considered in the previous sections will still apply for the second exposure, i.e. for *E*, provided the effect of *E* on *Y* is unconfounded conditional on *G* (and conditional on, if applicable, measured covariates *C*). Under this assumption of no confounding for *E*, we will still have that the total effect of *E* decomposes into the sum $(p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})P(G = 1)$ on the absolute risk scale, and we can use the sum of these two components as our estimate of the total effect. Likewise, the regression method in the previous section will still be applicable and $\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(G=1)}{(p_{01}-p_{00})+(p_{11}-p_{10}-p_{01}+p_{00})P(G=1)}$ would constitute the proportion of the effect attributable to interaction. And similarly on the ratio scale, $\frac{(RERI)P(G=1)}{(RR_{01}-1)+(RERI)P(G=1)}$ would still constitute the proportion of the effect attributable to interaction. The methods in the previous two sections still apply even if *G* affects *E*, or if *G* and *E* are otherwise correlated.

However, the decomposition of a total effect into a conditional effect and an interaction considered in previous sections do not apply directly for the first exposure *G*, when *G* affects *E*. Intuitively, this is because the effect of *G* on *Y* does not depend only on the presence or absence of *E*, but it is also the case that whether *E* is itself present (and thus whether the interaction operates) depends on *G*. Said another way, if *G* affects *E*, *E* is not simply an effect modifier for *G*, but it is also potentially a mediator for *G*. Our decompositions above are no longer applicable. An alternative decomposition does, however, hold. Specifically it can be shown (see Appendix) that, when *G* affects *E*, we have the following decomposition for the total effect of *G*:

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$$(p_{g=1}-p_{g=0})=(p_{10}-p_{00})+(p_{11}-p_{10}-p_{01}+p_{00})P(E=1|G=1)+(p_{01}-p_{00})\{P(E=1|G=1)-P(E=1|G=0)\}.$$

The decomposition of the total effect of G, $(p_{g=1} - p_{g=0})$, now consists of three components. We will consider each component in turn. The first component $(p_{10} - p_{00})$ is simply the effect of G in the absence of E i.e. the portion of the effect of G that would remain if E were fixed to 0. This is analogous to the first component in the two-way decompositions above. The second component, $(p_{11} - p_{10} - p_{01} + p_{00})P(E = 1|G = 1)$, is the effect attributable to interaction, but now the interaction term, $(p_{11} - p_{10} - p_{01} + p_{00})$, is multiplied by $P(E = 1|G = 1)$ when G affects E rather than being multiplied by $P(E = 1)$, as when G and E were independent; note when G and E are independent, $P(E = 1|G = 1)$ reduces to $P(E = 1)$. The third component, $(p_{01} - p_{00})\{P(E = 1|G = 1) - P(E = 1|G = 0)\}$, was absent from the two-way decomposition; it is essentially the main effect of E in the absence of G, $(p_{01} - p_{00})$, multiplied by the effect of G on E, $\{P(E = 1|G = 1) - P(E = 1|G = 0)\}$; it could be interpreted as a mediated main effect; note again when G and E are independent $P(E = 1|G = 1) - P(E = 1|G = 0) = 0$ and thus this third component vanishes. In the Appendix we further discuss the relationship between this decomposition and the decompositions in the mediation analysis literature.

Thus when G affects E, and we are decomposing the total effect of G two things happen to the decomposition we had under independence. First, because G affects E, we need to take into account the fact that the presence of E (and thus the possibility that the interaction between the two operates) is itself affected by G and thus the interaction term in the second component is multiplied by $P(E = 1|G = 1)$, rather than $P(E = 1)$. Second, when G affects E, a change in G from 0 to 1 will also change E and thus the main effect of E is more likely to operate and we thus introduce a third component, $(p_{01} - p_{00})\{P(E = 1|G = 1) - P(E = 1|G = 0)\}$ to the decomposition.

Under this setting of G affecting E, the proportion of the effect attributable to interaction becomes:

$$pAI_{E=0}(G)=\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(E=1|G=1)}{(p_{g=1}-p_{g=0})}.$$

In this context, we might also wonder what the consequences are of ignoring dependence between G and E and proceeding with estimating the proportion attributable to interaction measure when independence of G and E is (incorrectly) assumed, i.e. of using the measure

$$pAI_{E=0}(G)=\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(E=1)}{(p_{g=1}-p_{g=0})}.$$

It is shown in the Appendix that if the latter measure is used for the proportion attributable to interaction, incorrectly assuming independence, then although the latter measure does not actually capture the proportion of the effect attributable to interaction, it does nonetheless constitute a lower bound on the proportion of the effect of G that would be eliminated by fixing *E* to 0, provided *G* has a non-negative effect on *E*, and provided *E* has a non-negative effect on *Y* (at least in the absence of *G*). Thus even if one proceeds with the more naive estimate of the proportion attributable to interaction, ignoring (incorrectly) the dependence between *G* and *E*, one still, under fairly reasonable assumptions, obtains a lower bound on the proportion of the effect of *G* eliminated by fixing *E* to 0.

Further extensions to this approach of relaxing the assumption of independence are discussed in the Appendix. There this is generalized to non-binary exposures and outcomes, to the ratio scale, and to settings in which covariates are needed to control for confounding.

When *G* affects *E*, two other alternative approaches are worth noting. First instead of decomposing the total effect into a component due to interaction and the various main effects, one might alternatively use methods for mediation. If *G* affects *E* and *E* affects *Y*, then *E* will in general be a mediator for the effect of *G* on *Y*, and one can assess how much of the effect of *G* on *Y* is mediated by *E*. Methods for mediation and easy-to-use software packages[6,7] are now available to carry out such mediation analysis. These methods now also allow for interactions between the two exposures *G* and *E*.[7,8] Since these methods are described elsewhere we will not consider them in detail here. It should be noted, however, that these methods address different questions than the ones we have been considering in this paper. However, when *G* affects the second exposure *E*, the questions concerning mediation may be the more relevant questions of interest. One can use these methods to assess the proportion of the effect of *G* on *Y* mediated through *E*.

This proportion-mediated measure is related to, but not identical with, the proportion eliminated discussed above.[9,10] The proportion eliminated is not always identical to the proportion mediated because it considers what would happen if we fixed the second exposure (the mediator *E*) to a particular level (rather than allowing *G* to affect it). See VanderWeele[10] for further discussion. The decomposition above also gives an interpretation to the portion eliminated measure: it states that the difference between the total effect and the portion of the effect that would remain if *E* were fixed to zero is equal to the sum of the interaction term and the mediated main effect (i.e. the second and third terms in the decomposition above). Second, yet another approach to assess the importance of interaction with regard to *G* when *G* itself affects *E* is to decompose not a total effect of *G* on *Y*, but rather to focus on the joint effects of *G* and *E* together and to decompose this joint effect. This is the approach we consider in the following section.

Decomposition of Joint Effects into Main Effects and an Interactive Component

Another decomposition would be to decompose the joint effects of the two exposures, *G* and *E*, into three components, the effect due to *G* alone, the effect due to *E* alone and their interaction. On the risk difference scale this is

$$p_{11}-p_{00}=(p_{10}-p_{00})+(p_{01}-p_{00})+(p_{11}-p_{10}-p_{01}+p_{00}).$$

We could then also compute the proportion of the effect due to *G* alone, $\frac{(p_{10}-p_{00})}{(p_{11}-p_{00})}$, due to *E* alone, $\frac{(p_{01}-p_{00})}{(p_{11}-p_{00})}$, and due to their interaction, $\frac{(p_{11}-p_{10}-p_{01}+p_{00})}{(p_{11}-p_{00})}$. We can carry out a decomposition like this even if *G* affects *E*.

On the risk ratio scale, we can decompose the excess relative risk for both exposures RR_{11} − 1 into the excess relative risk for *G* alone, for *E* alone, and the excess relative risk due to interaction, *RERI*. Specifically we have

$$RR_{11}-1=(RR_{10}-1)+(RR_{01}-1)+RERI.$$

We could then likewise compute the proportion of the effect due to *G* alone, $\frac{RR_{10}-1}{RR_{11}-1}$, due to *E* alone, $\frac{RR_{01}-1}{RR_{11}-1}$, and due to their interaction $\frac{RERI}{RR_{11}-1}$.

Under the logistic regression model in (2) for an outcome that is rare, the joint effect attributable to *G* alone, *E* alone, and to their interaction are given approximately by:

$$\frac{RR_{10}-1}{RR_{11}-1}\approx\frac{e^{\gamma_1}-1}{e^{\gamma_1+\gamma_2+\gamma_3}-1}\;\frac{RR_{01}-1}{RR_{11}-1}\approx\frac{e^{\gamma_2}-1}{e^{\gamma_1+\gamma_2+\gamma_3}-1}\;\frac{RERI}{RR_{11}-1}\approx\frac{(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)}{e^{\gamma_1+\gamma_2+\gamma_3}-1}.$$

As discussed in the Appendix, these same expressions can be used even when control is made for covariates in the logistic regression. In the eAppendix we give standard errors for these proportion measures as well as SAS and Stata code to estimate the proportions and their standard errors and 95% confidence intervals.

Rothman[3] considered a measure of interaction that he called the attributable proportion, defined as $\frac{RERI}{RR_{11}}$; the denominator Rothman used was RR_{11}. The measure was meant to capture the proportion of the disease in the doubly exposed group that is due to the interaction. Rothman[3] also considered an alternative measure, $\frac{RERI}{RR_{11}-1}$, which captured the proportion of the effect of both exposures on the additive scale that is due to interaction. Most of the subsequent literature has focused on the former measure and likewise most of the other literature on attributable fractions focuses on the proportion of disease attributable to an exposure,[2] or to an interaction. However using the latter measure, i.e. using RR_{11} − 1, as the denominator, and focusing on the proportion of the effect due to interaction in fact has a number of advantages: both the numerator and the denominator are then on the additive excess relative risk scale; when the entirety of the effect is due to the interaction, the latter measure is then 100% and not some number less than 100%; and the latter measure is moreover invariant to recoding of the outcome.[11] Furthermore, as we have shown here, the latter measure is what is involved in the decomposition above. With Rothman's primary measure, $\frac{RERI}{RR_{11}}$, even if all of the joint effect were due to interaction so that the effect of *G* alone and E alone were both risk ratios of 1, i.e. $RR_{10} = 1$ and $RR_{01} = 1$, we would nevertheless have that Rothman's primary attributable proportion measure would be $\frac{RERI}{RR_{11}}=\frac{R_{11}-R_{10}-R_{01}+1}{RR_{11}}=\frac{R_{11}-1-1+1}{RR_{11}}=\frac{R_{11}-1}{RR_{11}}<1$; i.e. even if the entirety of the joint effect of both exposures were due to interaction, the attributable proportion measure is still less than 100%. The measure $\frac{RERI}{RR_{11}-1}$ does not have this issue. It is 100% when the main effects of G alone and E alone were both risk ratios of 1; i.e. when the entirety of the joint effect is due to interaction. The measure $\frac{RERI}{RR_{11}-1}$ captures the proportion of the joint effect attributable to interaction.

The attributable proportion of joint effects measure, $\frac{RERI}{RR_{11}-1}$, is also attractive from another standpoint. Skrondal[12] criticized Rothman's original attributable proportion measure because, in the presence of covariates, if the risks follow a linear risk model that is additive in the covariates, $P(Y = 1|G = g, E = e, C = c) = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 ge + \alpha_4 c$, then, although the additive interaction, $p_{11} - p_{10} - p_{01} + p_{00} = \alpha_3$, does not vary across strata of the covariates, Rothman's primary attributable proportion measure, $\frac{RERI}{RR_{11}}=\frac{\alpha_3}{\alpha_0+\alpha_1+\alpha_2+\alpha_3+\alpha_4 c}$, does vary across strata of the covariates. One may or may not think that this is an important criticism of the attributable proportion measure; however, attributable proportion measure for effect, $\frac{RERI}{RR_{11}-1}=\frac{\alpha_3}{\alpha_1+\alpha_2+\alpha_3}$, does not vary with the covariates and thus circumvents this criticism entirely.

Empirical Illustration

We illustrate the various decompositions with an example from genetic epidemiology. We use data from a case-control study of lung cancer at Massachusetts General Hospital (Miller et al.[13]) of 1836 cases and 1452 controls. Eligible cases included any person over the age of 18 years; the controls were recruited from among the friends or spouses of cancer patients or the friends or spouses of other surgery patients in the same hospital. The study included information on smoking and genotype information on locus 15q25.1. For simplicity in this illustration, we will code the exposure as binary so that smoking is ever vs. never and the genetic variant is a comparison of 0 vs. 1 or 2 T alleles at rs8034191. See the Appendix and eAppendix for approaches handling ordinal and categorical exposures. Covariate data include age (continuous), sex and educational history (college degree or more, yes / no). Analyses were restricted to white persons. Genetic variants on 15q25.1 have been found to be associated with both smoking and lung cancer[5,14,15] and thus we are in a setting in which the first exposure G is correlated with the second exposure E. The prevalences of the exposures among the controls (which approximates that of the underlying population since the outcome is rare) is $P(G = 1) = 56.7\%$ and $P(G = 1) = 64.94\%$. When we fit the logistic regression model in (2), adjusting also for covariates, we obtain estimates: $\gamma_1 = 0.04$ (95% CI= −0.33 to 0.41), $\gamma_2 = 1.33$ (1.01 to 1.64), $\gamma_3 = 0.49$ (0.08 to 0.89). The main effect of G is small, the main effect of E is large, and the interaction is of moderate size. If we use the regression coefficients to calculate the proportion attributable to interaction for *E* we obtain a proportion of 34.5% (7.1% to 61.9%). Even if we eliminated the genetic exposure, 65.5% of the effect would remain (34.5% would be eliminated). The results are summarized in the first two lines of the Table.

We could proceed with a similar analysis with *G* but because *G* affects *E* here we need to be somewhat more careful in interpretation. Here, however, the correlation between *G* and *E*, although present, is quite weak, and so the decomposition assuming independence might not be a bad approximation. If we proceed with the decomposition we obtain that the proportion of the effect of *G* due to interaction is 98% (58% to 137%). Almost all of the effect of *G* is due to the presence of *E* and its interaction with *E*. As discussed above if we can assume that the variants increase smoking, and that smoking increases lung cancer (both reasonable assumptions here), then 98% (95% CI= 58% to 137%) would be a lower bound on the proportion of the effect of *G* that would be eliminated if we were to eliminated smoking. And, indeed, there is now strong evidence elsewhere that the genetic variants do not have an effect on lung cancer for non-smokers.[16,17] Almost the entirety of the effect of *G* appears due to the interaction.

If we proceed with the decomposition of the joint effect, then the proportions attributable to *G* alone, *E* alone, and to their interaction are:

$$\frac{RR_{10}-1}{RR_{11}-1}\approx 0.8\%(95\%CI{=}{-6.2}\%\text{to}7.7\%)\ \frac{RR_{01}-1}{RR_{11}-1}\approx 51.4\%(33.4\%\text{to}69.4\%)\ \frac{RERI}{RR_{11}-1}\approx 47.8\%(33.3\%\text{to}62.3\%).$$

The results are summarized in the third line of the Table. Almost none of the joint effect (comparing both *G* and *E* present to both absent) is due to the effect of *G* in the absence of *E*, about 51% is due to *E* is the absence of *G*, and about 48% is due to the interaction between *G* and *E*. Note that the decompositions for total effects and for joint effects differ in their denominators and so are not directly comparable to each other: the decomposition for joint effect considers the proportion of the effect due to interaction when comparing both exposures present versus neither present; the decompositions for total effects considers the proportion of the effect due to interaction when one exposure is present (and the other is fixed at its actual level) versus when that same single exposure is absent.

Discussion

In this paper we have considered the decomposition of a total effect into a conditional effect when the other exposure is fixed to 0 and a component due to interaction. This decomposition can be done with both exposures if the two exposures are independent, but can be done only with the second exposure in settings in which the first exposure affects the second. Other decompositions for the first exposure are then possible, but the interpretation becomes somewhat more complicated. Even in this case, the joint effects of both exposures can still be decomposed into the component due to the first exposure alone, that due to the second exposure alone, and that due to their interaction. In the Appendix fairly general methods are given using linear regression for carrying out these decompositions with binary, ordinal or continuous exposures. In the eAppendix methods and software are provided for these decompositions using logistic regression and linear regression when the outcome is binary or outcomes and the exposures are binary or continuous. These various decompositions can shed light on the proportion of various effects that are attributable to interaction.

Several motivations are commonly given for assessing interaction: first, to identify subgroups for which an intervention on the exposure might be most effective in settings in which resources are limited[1–3,18]; second, to assess evidence for mechanistic forms of interaction[2,19–21]; third, to leverage interaction to increase power to detect genetic effect[22–24]; and fourth to allow for additional flexibility in statistical models.[2,25] The methods described in this paper suggest yet another motivation for assessing interaction. The methods here for attributing effects to interactions may help determine the extent to which an intervention on a potential effect modifier would successfully alter the effect of the exposure of interest. As noted above, one of the motivations often given for studying interaction, specifically on the additive scale, is to identify which subgroups would benefit most from intervention when resources are limited. However in some settings it may not be possible to intervene directly on the primary exposure of interest, and one might then instead be interested in which other covariates could be intervened upon to eliminate much or most of the effect of the primary exposure of interest. The methods here for attributing effects to interactions can be useful in assessing this and identifying the most relevant covariates for intervention.

When used for this purpose it is important that it is the effect modifier itself that affects the outcome and that the effect modifier is not simply serving as a proxy for some other variable that does.[26,27] In other words, we need to make sure we have controlled for confounding for the effects of the effect modifier itself. These issues of confounding control are discussed in greater detail in the Appendix. We have assumed throughout, for simplicity, that the effects of both factors are unconfounded, but these assumptions need to be thought about more carefully if these measures are to be used in making policy decisions. However, provided such control for confounding for both factors has been made, the measures considered in this paper can be useful in determining how much of an effect could be eliminated by intervening on an effect modifier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Decomposition of a Total Effect into a Conditional Effect and a Portion due to Interaction

We will let G and E denote two exposures of interest which may be binary, continuous or categorical and let Y be an outcome of interest that may be binary or continuous. Let Y_g denote the counterfactual outcome for an individual if G were set to g, let Y_e denote the counterfactual outcome for an individual if E were set to e, and let Y_{ge} denote the counterfactual outcome for an individual if G were set to g and E were set to e. We will say that the effect of G on Y is unconfounded conditional on C if $Y_g \perp\!\!\!\perp G|C$. We will say that the effect of E on Y is unconfounded conditional on C if $Y_e \perp\!\!\!\perp E|C$. We will say the joint effects of G and E on Y are unconfounded conditional on C if $Y_{ge} \perp\!\!\!\perp (G,E)|C$.

Proposition 1. For any two levels e_1 and e_0 of E and any level g_0 of G we have the decomposition:

$$\mathbb{E}[Y_{e_1}-Y_{e_0}|c]=\mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c]+\int\{\mathbb{E}[Y_{e_1}-Y_{e_0}|g,c]-\mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c]\}dP(g|c).$$

Proof. We have

$$\begin{aligned}\mathbb{E}[Y_{e_1}-Y_{e_0}|c] &= \mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c] + \mathbb{E}[Y_{e_1}-Y_{e_0}|c] - \mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c] \\ &= \mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c] + \int\{\mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c]-\mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c]\}dP(g|c).\end{aligned}$$

In Proposition 1, we can decompose a total effect, $\mathbb{E}Y_{e_1} - Y_{e_0}|c]$, into an effect conditional on $G = g_0$, namely, $\mathbb{E}Y_{e_1} - Y_{e_0}|g_0, c]$, and a component which is a summary measure of effect modification, $\int \{\mathbb{E}Y_{e_1} - Y_{e_0}|g, c] - \mathbb{E}Y_{e_1} - Y_{e_0}|g_0, c]\}dP(g|c)$. The proportion attributable to interaction is then defined by

$$pAI_{G=g_0}(E)=\frac{\int\{\mathbb{E}[Y_{e_1}-Y_{e_0}|g,c]-\mathbb{E}[Y_{e_1}-Y_{e_0}|g_0,c]\}dP(g|c)}{\mathbb{E}[Y_{e_1}-Y_{e_0}|c]}$$

. The decomposition here is given at the counterfactual level and, as noted above, it is a decomposition of a total effect into an effect conditional on G and a measure of effect modification. Note that this decomposition and the proportion due to interaction will vary for different values of $G = g_0$ and thus the reference value g_0 must be specified. This reference value was taken as $G = 0$ in the text; it is the value at which the conditional effect, $\mathbb{E}Y_{e_1} - Y_{e_0}|g_0, c]$, is estimated. The decomposition is given for a particular level of the covariates $C = c$ but we can also marginalize over C to obtain $\mathbb{E}Y_{e_1} - Y_{e_0}] = \int \mathbb{E}Y_{e_1} - Y_{e_0}|g_0, c]dP(c)+ \int \{\mathbb{E}Y_{e_1}-Y_{e_0}|g, c] - \mathbb{E}$

$Y_{e1} - Y_{e0}|g_0, c]\}dP(g, c)$. Note then, however, that the first term in the decomposition, $\int \mathbb{E} Y_{e1} - Y_{e0}|g_0, c]dP(c)$, is the effect of E on Y conditional on $G = g_0$, and marginalized over the distribution $P(C)$. It will not in general equal $\mathbb{E}Y_{e1} - Y_{e0}\,|g_0]$ since $\mathbb{E}Y_{e1} - Y_{e0}|g_0, c]$ is marginalized over $P(C)$ rather than $P(C|g_0)$.

Under assumptions about confounding we can identify each component of the decomposition.

Proposition 2. Suppose that the effect of E on Y is unconfounded conditional on (C,G) then:

$$\mathbb{E}[Y_{e_1} - Y_{e_0}|g, c] = \mathbb{E}[Y|g, e_1, c] - \mathbb{E}[Y|g, e_0, c]$$

and we can thus identify the components in Proposition 1 and the right hand-side of the decomposition in Proposition 1 can be written in terms of observed data as: $\mathbb{E}Y_{e1} - Y_{e0}\,|c]$

$$= \mathbb{E}[Y|g_0, e_1, c] - \mathbb{E}[Y|g_0, e_0, c] + \int \{\mathbb{E}[Y|g, e_1, c] - \mathbb{E}[Y|g, e_0, c] - \mathbb{E}[Y|g_0, e_1, c] + \mathbb{E}[Y|g_0, e_0, c]\} dP(g|c).$$

If, moreover, the joint effects of G and E are unconfounded conditional on C then we can write the decomposition as:

$$\mathbb{E}[Y_{e_1} - Y_{e_0}|c] = \mathbb{E}[Y_{g_0 e_1}|c] - \mathbb{E}[Y_{g_0 e_0}|c] + \int \{\mathbb{E}[Y_{g e_1}|c] - \mathbb{E}[Y_{g e_0}|c] - \mathbb{E}[Y_{g_0 e_1}|c] + \mathbb{E}[Y_{g_0 e_0}|c]\} dP(g|c).$$

Proof. If the effect of E on Y is unconfounded conditional on (C,G), then we have $\mathbb{E}Y_{e1} - Y_{e0}\,|g, c] = \mathbb{E}Y\,|g, e_1, c] - \mathbb{E}Y\,|g, e_0, c]$. If the joint effects of G and E are unconfounded conditional on C then we have $\mathbb{E}Y|g, e, c] = \mathbb{E}Y_{ge}|c]$ and thus:

$$\mathbb{E}[Y_{e_1} - Y_{e_0}|c] = \mathbb{E}[Y_{g_0 e_1}|c] - \mathbb{E}[Y_{g_0 e_0}|c] + \int \{\mathbb{E}[Y_{g e_1}|c] - \mathbb{E}[Y_{g e_0}|c] - \mathbb{E}[Y_{g_0 e_1}|c] + \mathbb{E}[Y_{g_0 e_0}|c]\} dP(g|c).$$

If the effect of E on Y is unconfounded conditional on C alone as would be the case under Proposition 2 if G and E were independent conditional C then we would also have $\mathbb{E}Y_{e1} - Y_{e0}|c] = \mathbb{E}Y|e_1, c] - \mathbb{E}Y|e_0, c]$. Otherwise, we will not have $\mathbb{E}Y_{e1} - Y_{e0}|c] = \mathbb{E}Y|e_1, c] - \mathbb{E}Y|e_0, c]$, but we could still obtain $\mathbb{E}Y_{e1} - Y_{e0}|c]$ under Proposition 2 using the sum of the two components, $\mathbb{E}Y|g_0, e_1, c] - \mathbb{E}Y|g_0, e_0, c]$ and $\int \{\mathbb{E}Y|g, e_1, c] - \mathbb{E}Y|g, e_0, c] - \mathbb{E}Y|g_0, e_1, c] + \mathbb{E} Y|g_0, e_0, c]\}dP(g)$.

Note that in the second part of Proposition 2, to obtain the decomposition, $\mathbb{E}Y_{e1} - Y_{e0}|c] = \mathbb{E} Y_{g0e1}|c] - \mathbb{E}Y_{g0e0}|c] + \int \{\mathbb{E}Y_{ge1}|c] - \mathbb{E}Y_{ge0}|c] - \mathbb{E}Y_{g0e1}|c] + \mathbb{E}Y_{g0e0}|c]\}dP(g|c)$, we required that joint effects of both G and E on Y were unconfounded given C. Under this assumption, what we estimate as the portion attributable to interaction is equal to the difference, $\mathbb{E}Y_{e1} - Y_{e0}|c] - \{\mathbb{E}Y_{g0e1}|c] - \mathbb{E}Y_{g0e0}|c]\}$ i.e. to the portion of the effect of E on Y that could be eliminated if we fixed G to g_0. This measure may be of relevance from a policy perspective insofar as we can determine the extent to which intervening to fix G to some level g_0 would eliminate the effect of E on the outcome. We might thus decide whether to intervene on G in order to eliminate the effect of E. Importantly, however, to interpret the measure in this manner it is important that control is made for confounding for both exposures, G and E.

Viewed intuitively, this ensures that it is the effect modifier itself that affects the outcome and that the effect modifier is not simply serving as a proxy for some other variable that does.[26,27] When this is the case the proportion attributable to interaction is equal to the proportion eliminated by fixing G to g_0.

If no covariates are necessary for confounding control and we let $p_{ge} = P(Y = 1|G = g, E = e)$, $p_g = P(Y = 1|G = g)$, and $p_e = P(Y = 1|E = e)$ then the first decomposition in Proposition 2 written in terms of the observed data simplifies to:

$$(p_{e=1} - p_{e=0}) = (p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})P(G=1).$$

and the second decomposition written in terms of counterfactuals simplifies to

$$\mathbb{E}[Y_{e=1} - Y_{e=0}] = \mathbb{E}[Y_{01} - Y_{00}|c] + \mathbb{E}[Y_{11} - Y_{10} - Y_{01} + Y_{00}]P(G=1).$$

For the linear model

$$\mathbb{E}[Y|G=g, E=e, C=c] = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 eg + \alpha_4^{'} c,$$

we have

$$\mathbb{E}[Y|g, e_1, c] - \mathbb{E}[Y|g, e_0, c] = (\alpha_0 + \alpha_1 g + \alpha_2 e_1 + \alpha_3 e_1 g + \alpha_4^{'} c) - (\alpha_0 + \alpha_1 g + \alpha_2 e_0 + \alpha_3 e_0 g + \alpha_4^{'} c) = (\alpha_2 + g\alpha_3)(e_1 - e_0)$$

and thus the first component in the empirical decomposition in Proposition 2 is equal to:

$$\mathbb{E}[Y|g_0, e_1, c] - \mathbb{E}[Y|g_0, e_0, c] = (\alpha_2 + g_0\alpha_3)(e_1 - e_0)$$

and the second is equal to:

$$\begin{aligned}\int \{\mathbb{E}[Y|g, e_1, c] & \\ & - \mathbb{E}[Y|g, e_0, c] \\ & - \mathbb{E}[Y|g_0, e_1, c] \\ & + \mathbb{E}[Y|g_0, e_0, c]\} dP(g|c) = \int (\alpha_2 + g\alpha_3)(e_1 - e_0) - (\alpha_2 + g_0\alpha_3)(e_1 - e_0) dP(g|c) = \alpha_3\{\mathbb{E}[G|c] \\ & \quad - g_0\}(e_1 - e_0).\end{aligned}$$

The proportion due to interaction is then $\frac{\alpha_3\{\mathbb{E}[G|c] - g_0\}}{(\alpha_2 + \alpha_3\mathbb{E}[G|c])}$. When G and E are binary and $g_0 = 0$ and there are no covariates, the two components reduce to α_2 and $\alpha_3 P(G = 1)$ and the proportion due to interaction is $\frac{\alpha_3 P(G=1)}{\alpha_2 + \alpha_3 P(G=1)}$, as in the text. Note, however, that when the exposures are not binary the measures themselves (and thus the proportion attributable to interaction) may vary depending on the values, e_1 and e_0, of E that are being compared, also and also again on the reference value, g_0 of G.

On the risk ratio scale, we let $RR_{g=1}=\frac{p_{g=1}}{p_{g=0}}=\frac{P(Y=1|G=1)}{P(Y=1|G=0)}$ and $RR_{e=1}=\frac{p_{e=1}}{p_{e=0}}=\frac{P(Y=1|E=1)}{P(Y=1|E=0)}$ and $RR_{ge}=\frac{p_{ge}}{p_{00}}=\frac{P(Y=1|G=g,E=e)}{P(Y=1|G=0,E=0)}$. The decomposition $(p_{e=1} - p_{e=0}) = (p_{01} - p_{00}) + (p_{11} - p_{10} - p_{01} + p_{00})P(G = 1)$ when divided by $p_{e=0}$ is

$$(RR_{e=1}-1)=\kappa(RR_{01}-1)+\kappa(RR_{11}-RR_{10}-RR_{01}+1)P(G=1).$$

where κ is a scaling factor given by $\kappa=\frac{p_{00}}{p_{e=0}}$. The proportion of the effect of E attributable to interaction is given by:

$$pAI_{G=0}(E)=\frac{(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}{(RR_{01}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}.$$

As noted in the text, if we use the logistic regression model

$$logit\{P(Y=1|G=g,E=e,C=c)\}=\gamma_0+\gamma_1 g+\gamma_2 e+\gamma_3 eg+\gamma_4' c.$$

then proportion attributed to interaction if the exposures are binary can be approximated by $pAI_{G=0}(E)\approx\frac{(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)}{(e^{\gamma_2}-1)+(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)P(G=1)}$. In the eAppendix we discuss estimating standard errors for this proportion attributed to interaction.

Analogous Results for G

Note that, by symmetry, from Proposition 1, we have the decomposition

$$\mathbb{E}[Y_{g_1}-Y_{g_0}|c]=\mathbb{E}[Y_{g_1}-Y_{g_0}|e_0,c]+\int\{\mathbb{E}[Y_{g_1}-Y_{g_0}|e,c]-\mathbb{E}[Y_{g_1}-Y_{g_0}|e_0,c]\}dP(e|c).$$

This decomposition applies even if G affects E. If G and E were independent so that G did not affect E, then we would have an analogue of Proposition 2 which would be that if the effect of G on Y is unconfounded conditional on (C, E) then we have $\mathbb{E}Y_{g1} - Y_{g0}|e, c] = \mathbb{E}Y|g_1, e, c]- \mathbb{E}Y|g_0, e, c]$, and under independence also, $\mathbb{E}Y_{g1} - Y_{g0}|c] = \mathbb{E}Y|g_1, c] - \mathbb{E}[Y|g_0, c]$, and we can thus write the decomposition of the total effect of G in terms of observed data as: $\mathbb{E}Y|g_1, c] - \mathbb{E}Y|g_0, c]$

$$=\mathbb{E}[Y|g_1,e_0,c]-\mathbb{E}[Y|g_0,e_0,c]+\int\{\mathbb{E}[Y|g_1,e,c]-\mathbb{E}[Y|g_0,e,c]-\mathbb{E}[Y|g_1,e_0,c]+\mathbb{E}[Y|g_0,e_0,c]\}dP(e|c).$$

If, moreover, the joint effects of *G* and *E* are unconfounded conditional on *C* then we can write the decompositions as:

$$\mathbb{E}[Y_{g_1} - Y_{g_0}|c] = \mathbb{E}[Y_{g_1e_0} - Y_{g_0e_0}|c] + \int\{\mathbb{E}[Y_{g_1e} - Y_{g_0e}|c] - \mathbb{E}[Y_{g_1e_0} - Y_{g_0e_0}|c]\}dP(e|c).$$

Settings in which G Affects E

If *G* affects *E*, then the conditions in Proposition 2 still apply. We can still thus empirically decompose the total effect of *E* on *Y* into a conditional effect and the portion due to interaction. If *G* affects *E* we no longer have the simple relation $[Y_{e_1} - Y_{e_0}|c] = \mathbb{E}Y|e_1, c] - \mathbb{E}Y|e_0, c]$ because control for *G* will in general be needed to control for confounding for *E*. But we can still obtain $\mathbb{E}Y_{e_1} - Y_{e_0}|c]$, even if *G* affects *E* under Proposition 2, using the sum of the two components, $\mathbb{E}Y|g_0, e_1, c] - \mathbb{E}Y|g_0, e_0, c]$ and $\int\{\mathbb{E}Y|g, e_1, c] - \mathbb{E}Y|g, e_0, c] - \mathbb{E}Y|g_0, e_1, c] + \mathbb{E}Y|g_0, e_0, c]\}dP(g)$.

However, if *G* affects *E* then the analogue of Proposition 2 for *G* will not apply. We still have the analogous decomposition to that in Proposition 1:

$$\mathbb{E}[Y_{g_1} - Y_{g_0}|c] = \mathbb{E}[Y_{g_1} - Y_{g_0}|e_0, c] + \int\{\mathbb{E}[Y_{g_1} - Y_{g_0}|e, c] - \mathbb{E}[Y_{g_1} - Y_{g_0}|e_0, c]\}dP(e|c).$$

However, the counterfactuals of the form $\mathbb{E}Y_{g_1} - Y_{g_0}|e_0, c]$ will not be identified and so we cannot empirically estimate the various parts of the decomposition. This is because when *G* affects *E*, the analogue Proposition 2 for *G* would require that the effect of *G* on *Y* is unconfounded on (*C*, *E*) and this fails because *G* itself affects *E*.

However, when *G* affects *E* we still have the decomposition in the Proposition below.

Proposition 3. If the effect of *G* on *Y* is unconfounded conditional on *C*, and the effects of *G* and *E* are unconfounded conditional on *C* then we have

$$\begin{aligned}\mathbb{E}[Y_{g_1} - Y_{g_0}|c] &= \mathbb{E}[Y_{g_1e_0} - Y_{g_0e_0}|c] \\ &+ \int\{\mathbb{E}[Y_{g_1e} - Y_{g_0e}|c] - \mathbb{E}[Y_{g_1e_0} - Y_{g_0e_0}|c]\}dP(e|g_1, c) \\ &+ \int\{\mathbb{E}[Y_{g_0e} - Y_{g_0e_0}|c]\}\{dP(e|g_1, c) - dP(e|g_0, c)\}.\end{aligned}$$

Moreover, each component of the decomposition above identified and the corresponding decomposition expressed in terms of the observed data is $\mathbb{E}Y_{g_1} - Y_{g_0}|c]$

$$
\begin{aligned}
=&\{\mathbb{E}[Y|g_1,e_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\} \\
&+ \int\{\mathbb{E}[Y|g_1,e,c] \\
&- \mathbb{E}[Y|g_0,e,c]\} - \{\mathbb{E}[Y|g_1,e_0,c] - \mathbb{E}[Y|g_0,e_0,c]\}dP(e|g_1,c) \\
&+ \int\{\mathbb{E}[Y|g_0,e,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\}\{dP(e|g_1,c) \\
&- dP(e|g_0,c)\}.
\end{aligned}
$$

Proof. We have that $\mathbb{E}Y_{g1} - Y_{g0}|c]$

$$
\begin{aligned}
=&\mathbb{E}[Y|g_1,c] \\
&- \mathbb{E}[Y|g_0,c] \\
=&\mathbb{E}[Y|g_1,e_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c] \\
&+\{\mathbb{E}[Y|g_1,c] \\
&- \mathbb{E}[Y|g_1,e_0,c]\} \\
&- \{E[Y|g_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\} \\
=&\mathbb{E}[Y|g_1,e_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c] \\
&+\int\{\mathbb{E}[Y|g_1,e,c] \\
&- \mathbb{E}[Y|g_1,e_0,c]\}dP(e|g_1,c) \\
&- \int\{\mathbb{E}[Y|g_0,e,c] - \mathbb{E}[Y|g_0,e_0,c]\}dp(e|g_0,c) \\
=&\{\mathbb{E}[Y|g_1,e_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\} \\
&+\int\{\mathbb{E}[Y|g_1,e,c] \\
&- \mathbb{E}[Y|g_0,e,c]\} - \{\mathbb{E}[Y|g_1,e_0,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\}dP(e|g_1,c) \\
&+\int\{\mathbb{E}[Y|g_0,e,c] \\
&- \mathbb{E}[Y|g_0,e_0,c]\}\{dP(e|g_1,c) - dP(e|g_0,c)\} \\
=&\mathbb{E}[Y_{g_1e_0} \\
&- Y_{g_0e_0}|c] \\
&+\int\{\mathbb{E}[Y_{g_1e} \\
&- Y_{g_0e}|c] \\
&- \mathbb{E}[Y_{g_1e_0} \\
&- Y_{g_0e_0}|c]\}dP(e|g_1,c) \\
&+\int\{\mathbb{E}[Y_{g_0e} \\
&- Y_{g_0e_0}|c]\}\{dP(e|g_1,c) \\
&- dP(e|g_0,c)\}.
\end{aligned}
$$

In the decomposition above, the first term, $\mathbb{E}Y_{g_1e_0} - Y_{g_0e_0}|c] = \{\mathbb{E}Y|g_1, e_0, c] - \mathbb{E}Y|g_0, e_0, c]\}$ is the controlled direct effect[9,10] of G, comparing levels, g_1 and g_0, when E is fixed to e_0. The second term, $\int \{\mathbb{E}Y_{g_1e} - Y_{g_0e}|c] - \mathbb{E}Y_{g_1e_0} - Y_{g_0e_0}|c]\}dP(e|g_1, c)$, is the portion attributable to interaction; it is an interaction, $\mathbb{E}Y_{g_1e} - Y_{g_0e}|c] - \mathbb{E}Y_{g_1e_0} - Y_{g_0e_0}|c]$, standardized by the distribution, $P(e|g_1, c)$. The third and final term, $\int \{\mathbb{E}Y_{g_0e} - Y_{g_0e_0}|c]\} \{dP(e|g_1, c) - dP(e|g_0, c)\}$, is the main effect of E when $G = g_0$, standardized by $P(e|g_1, c)$ versus $P(e|g_0, c)$, which, provided the effect of G on E is unconfounded conditional on C, is essentially the effect of G on E and thus the third term is in some sense a mediated main effect.

When G, E and Y are binary and $g_0 = 0$ is selected as the reference level, and no covariates are required for confounding, the decomposition reduces to: $\mathbb{E}Y_1 - Y_0]$

$$=\mathbb{E}[Y_{10}-Y_{00}]+\mathbb{E}[Y_{11}-Y_{01}-Y_{10}-Y_{00}]P(E=1|G=1)+\mathbb{E}[Y_{01}-Y_{00}]\{P(E=1|G=1)-P(E=1|G=0)\}.$$

Or, expressed in terms of the observed data, as $(p_{g=1} - p_{g=0})$

$$=(p_{10}-p_{00})+(p_{11}-p_{10}-p_{01}+p_{00})P(E=1|G=1)+(p_{01}-p_{00})\{P(E=1|G=1)-P(E=1|G=0)\}$$

as in the text. The proportion attributable to interaction is then:

$$pAI_{E=0}(G)=\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(E=1|G=1)}{(p_{g=1}-p_{g=0})}.$$

Note that when G has a non-negative effect on E, and E has a non-negative effect on Y (in the absence of G) so that $P(E = 1|G = 1) - P(E = 1|G = 0) \geq 0$ and thus $P(E = 1) = P(E = 1|G = 1)P(G = 1) + P(E = 1|G = 0)P(G = 0) \leq P(E = 1|G = 1)$ and $(p_{01} - p_{00})\{P(E = 1|G = 1) - P(E = 1|G = 0)\} \geq 0$ we then have that $(p_{11} - p_{10} - p_{01} + p_{00})P(E = 1) \leq (p_{11} - p_{10} - p_{01} + p_{00})P(E = 1|G = 1) = (p_{g=1} - p_{g=0}) - (p_{10} - p_{00}) - (p_{01} - p_{00})\{P(E = 1|G = 1) - P(E = 1|G = 0)\} \leq (p_{g=1} - p_{g=0}) - (p_{10} - p_{00})$ and from this it follows that if the dependence between G and E is incorrectly ignored and

$$\frac{(p_{11}-p_{10}-p_{01}+p_{00})P(E=1)}{(p_{g=1}-p_{g=0})}.$$

is used for the proportion attributable to interaction, then although the latter measure does not actually capture the proportion of the effect attribution to interaction, it does nonetheless constitute a lower bound on the proportion of the effect of G that would be eliminated by fixing E to 0, as indicated in the text. Thus even if one proceeds with the more naive estimate of the proportion attributable to interaction, ignoring (incorrectly) the dependence between G and E one still, under fairly reasonable assumptions, obtains a lower bound on the proportion of the effect of G eliminated by fixing E to 0.

The decomposition in Proposition 3 with binary exposures when the effect of G on Y and on E are unconfounded, and the effects of (G, E) on Y are unconfounded can be rewritten as: $\mathbb{E}Y_1-Y_0] = \mathbb{E}Y_{10}-Y_{00}]+\mathbb{E}Y_{11}-Y_{01}-Y_{10}-Y_{00}]P(E_{g=1} = 1) + \mathbb{E}Y_{01}-Y_{00}]\{P(E_{g=1} = 1)-P(E_{g=0} = 1)\}$ where E_g is the counterfactual outcome for E fixing G to g. The analogue on the individual counterfactual level is $Y_1 - Y_0 = (Y_{10} - Y_{00}) + (Y_{11} - Y_{01} - Y_{10} - Y_{00})E_{g=1} + (Y_{01} - Y_{00})(E_{g=1} - E_{g=0})$. These are 3-way decompositions of a total effect. These differ somewhat from the decompositions in the mediation analysis literature.[6–9] In the mediation analysis literature, the total effect is decomposed into either two components, what is called a natural indirect effect and a natural direct effect given respectively by $\mathbb{E}Y_{1E_1}-Y_{1E_0}]$ and $\mathbb{E}Y_{1E_0}-Y_{0E_0}]$ respectively; or into three components[8], a so-called pure indirect effect,[9] a pure direct effect (equivalent to the natural direct effect just given), and a mediated interaction, which, when identified can be written as $\mathbb{E}Y_{0E_1} - Y_{0E_0}]$, $\mathbb{E}Y_{1E_0} - Y_{0E_0}]$, and $\mathbb{E}Y_{11}-Y_{01}-Y_{10}-Y_{00}]$, respectively. In contrast, for the decomposition given in Proposition 3, the "direct effect" given in this decomposition is a controlled direct effect, $\mathbb{E}Y_{10} - Y_{00}]$, not a natural direct effect; and the interaction term, $\mathbb{E}Y_{11}-Y_{01}-Y_{10}-Y_{00}]P(E_{g=1} = 1)$, is the proportion of the effect attributable to interaction. Note also that if G does not affect E (i.e. if there is no mediation) then the mediation decomposition into three components[8] reduces to a single component (the pure direct effect). However if G does not affect E, then, with the decompositions considered in this paper, there are still two components: the controlled direct effect for G and also the interaction term.

For the ratio scale, the decomposition, $(p_{g=1}-p_{g=0}) = (p_{10}-p_{00}) + (p_{11}-p_{10}-p_{01}+p_{00})P(E = 1|G = 1) + (p_{01} - p_{00})\{P(E = 1|G = 1) - P(E = 1|G = 0)\}\{P(E_{g=1} = 1) - P(E_{g=0} = 1)\}$, when divided by $p_{g=0}$ is

$$(RR_{g=1}-1)=\kappa(RR_{10}-1)+\kappa(RR_{11}-RR_{10}-RR_{01}+1)P(E=1|G=1)+\kappa(RR_{01}-1)\{P(E=1|G=1)-P(E=1|G=0)\}.$$

where κ is a scaling factor given by $\kappa=\frac{p_{00}}{p_{e=0}}$. The proportion of the effect of G attributable to interaction is:

$$pAI_{E=0}(G)=\frac{(RR_{11}-RR_{10}-RR_{01}+1)P(E=1|G=1)}{(RR_{10}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(E=1|G=1)+(RR_{01}-1)\{P(E=1|G=1)-P(E=1|G=0)\}}.$$

Decomposition of Joint Effects

At the counterfactual level, we can decompose the joint effects of the two exposures, G and E, into the effect due to G alone, the effect due to E alone and their interaction. We have:

$$\mathbb{E}[Y_{g_1e_1}-Y_{g_0e_0}|c]=\mathbb{E}[Y_{g_1e_0}-Y_{g_0e_0}|c]+\mathbb{E}[Y_{g_0e_1}-Y_{g_0e_0}|c]+\mathbb{E}[Y_{g_1e_1}-Y_{g_1e_0}-Y_{g_0e_1}+Y_{g_0e_0}|c]$$

If the joint effects of G and E are unconfounded conditional on C each of these components is identified from the observed data and the decomposition can be rewritten as:

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$$\begin{aligned}
&\mathbb{E}[Y|g_1,e_1,c]\\
&\quad-\mathbb{E}[Y|g_0,e_0,c]\\
&\quad=\{\mathbb{E}[Y|g_1,e_0,c]\\
&\qquad-\mathbb{E}[Y|g_0,e_0,c]\}\\
&\quad+\{\mathbb{E}[Y|g_0,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]\}\\
&\quad+\{\mathbb{E}[Y|g_1,e_1,c]\\
&\quad-\mathbb{E}[Y|g_1,e_0,c]\\
&\quad-\mathbb{E}[Y|g_0,e_1,c]\\
&\qquad+\mathbb{E}[Y|g_0,e_0,c]\}.
\end{aligned}$$

We can then also compute the proportion of the joint effect due *G* alone as $\frac{\mathbb{E}[Y|g_1,e_0,c]-\mathbb{E}[Y|g_0,e_0,c]}{\mathbb{E}[Y|g_1,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]}$, due to *E* alone as $\frac{\mathbb{E}[Y|g_0,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]}{\mathbb{E}[Y|g_1,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]}$, and due to their interaction as $\frac{\mathbb{E}[Y|g_1,e_1,c]-\mathbb{E}[Y|g_1,e_0,c]-\mathbb{E}[Y|g_0,e_1,c]+\mathbb{E}[Y|g_0,e_0,c]}{\mathbb{E}[Y|g_1,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]}$. Dividing the first decomposition above by $\mathbb{E}Y_{g0e0}|c]$, or the second by $\mathbb{E}Y|g_0, e_0, c]$, or both the numerator and the denominator of the proportions by $\mathbb{E}Y|g_0, e_0, c]$ yields decompositions and proportions on the ratio scale. All of these decompositions are applicable even if *G* affects *E*.

On a difference scale, under the linear model

$$\mathbb{E}[Y|G=g,E=e,C=c]=\alpha_0+\alpha_1 g+\alpha_2 e+\alpha_3 eg+\alpha_4^{'}c,$$

we have that the three components are given by:

$$\begin{aligned}
\{\mathbb{E}[Y|g_1,e_0,c]-\mathbb{E}[Y|g_0,e_0,c]\}\quad&=(\alpha_1+\alpha_3 e_0)(g_1-g_0)\\
\{\mathbb{E}[Y|g_0,e_1,c]-\mathbb{E}[Y|g_0,e_0,c]\}\quad&=(\alpha_2+\alpha_3 g_0)(e_1-e_0)\\
\{\mathbb{E}[Y|g_1,e_1,c]-\mathbb{E}[Y|g_1,e_0,c]-\mathbb{E}[Y|g_0,e_1,c]+\mathbb{E}[Y|g_0,e_0,c]\}\quad&=\alpha_3(g_1e_1-g_1e_0-g_0e_1+g_0e_0).
\end{aligned}$$

When *G* and *E* are binary, these three components reduce to α_1, α_2, and α_3, respectively. Note, however, that when the exposures are not binary the measures themselves (and thus the proportion attributable to each component) may vary depending on the values, e_1 and e_0, of *E* and the values, g_1 and g_0, of *G* that are being compared.

On a ratio scale, under the logistic regression model with a rare outcome,

$$logit\{P(Y=1|G=g,E=e,C=c)\}=\gamma_0+\gamma_1 g+\gamma_2 e+\gamma_3 eg+\gamma_4^{'}c$$

if *G* and *E* then the proportions discussed in the text of the joint effect attributable to *G* alone, *E* alone, and to their interaction are given approximately by:

$$\frac{RR_{10}-1}{RR_{11}-1} \approx \frac{e^{\gamma_1}-1}{e^{\gamma_1+\gamma_2+\gamma_3}-1}\ \frac{RR_{01}-1}{RR_{11}-1} \approx \frac{e^{\gamma_2}-1}{e^{\gamma_1+\gamma_2+\gamma_3}-1}\ \frac{RERI}{RR_{11}-1} \approx \frac{(e^{\gamma_1+\gamma_2+\gamma_3}-e^{\gamma_1}-e^{\gamma_2}+1)}{e^{\gamma_1+\gamma_2+\gamma_3}-1},$$

respectively. See the eAppendix for standard errors.

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Table

Summary of Results for the Empirical Illustration* on Proportion of the Total Effect of E due to Interaction (36.6%), the Total Effect of G due to Interaction (98.1%) and the Joint Effects of G and E due to Interaction (47.1%).

Decomposition	Components	Empirical Estimates
The Effect of E	$\frac{(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}{(RR_{01}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}+\frac{(RR_{01}-1)}{(RR_{01}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}$	34.5% + 65.5% = 100%
The Effect of G	$\frac{(RR_{11}-RR_{10}-RR_{01}+1)P(E=1)}{(RR_{10}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(G=1)}+\frac{(RR_{10}-1)}{(RR_{10}-1)+(RR_{11}-RR_{10}-RR_{01}+1)P(E=1)}$	97.6% + 2.4% = 100%
The Joint Effects	$\frac{RR_{10}-1}{RR_{11}-1}+\frac{RR_{01}-1}{RR_{11}-1}+\frac{RERI}{RR_{11}-1}$	0.8% + 51.4% + 47.8% = 100%

* The estimates and components are all also conditional on measured covarates (age, sex and educational history), omitted from the notation in the second column to conserve space