

The Interaction Continuum

Tyler J. VanderWeele

Abstract: A common reason given for assessing interaction is to evaluate “whether the effect is larger in one group versus another”. It has long been known that the answer to this question is scale dependent: the “effect” may be larger for one subgroup on the difference scale, but smaller on the ratio scale. In this article, we show that if the relative magnitude of effects across subgroups is of interest then there exists an “interaction continuum” that characterizes the nature of these relations. When both main effects are positive then the placement on the continuum depends on the relative magnitude of the probability of the outcome in the doubly exposed group. For high probabilities of the outcome in the doubly exposed group, the interaction may be positive-multiplicative positive-additive, the strongest form of positive interaction on the “interaction continuum”. As the probability of the outcome in the doubly exposed group goes down, the form of interaction descends through ranks, of what we will refer to as the following: positive-multiplicative positive-additive, no-multiplicative positive-additive, negative-multiplicative positive-additive, negative-multiplicative zero-additive, negative-multiplicative negative-additive, single pure interaction, single qualitative interaction, single-qualitative single-pure interaction, double qualitative interaction, perfect antagonism, inverted interaction. One can thus place a particular set of outcome probabilities into one of these eleven states on the interaction continuum. Analogous results are also given when both exposures are protective, or when one is protective and one causative. The “interaction continuum” can allow for inquiries as to relative effects sizes, while also acknowledging the scale dependence of the notion of interaction itself.

Keywords: Effect heterogeneity; Effect modification; Effect scale; Interaction

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Motivations for examining interaction include targeting subgroups to maximize public health impact when resources are constrained,^{1–7} determining optimal treatment assignments even when resources are not constrained,^{8–16} evaluating mechanisms,^{4–6,17–26} identifying effect modifiers to eliminate exposure effects,^{5,6,27,28} and assessing generalizability.^{29–36} Much has been learned in the past decades about the types of interaction analyses that should be used to pursue these various motivations.^{5,6} However, it is perhaps still the case that the most common reason given for assessing interaction is to evaluate “whether the effect is larger in one group versus another”. It has, however, been noted in the epidemiologic literature for decades, that the answer to this question is scale dependent.^{1–5,37–40} The effect may be larger in one subgroup than another on the difference scale, but smaller on the multiplicative risk ratio scale.^{4,5,38–40} Sometimes the relative comparison across groups will be the same, but sometimes they will not.³⁸ When speaking of smaller or larger effects across subgroups, one must thus specify the scale; some authors thus encourage the use of expressions such as “effect-measure modification”³⁸ so as to make clear the dependence of comparative effect sizes on the scale under consideration. Although these points are well-established, and are mathematical facts, they are often ignored in practice⁴¹ with absolute language about the effect being “larger” in one group than in another, or about an interaction being “present”, without any acknowledgment that these statements may be scale dependent.

With this motivation for interaction of comparing the magnitude of effect sizes across groups in mind, this article puts forward a notion of an “interaction continuum” that acknowledges not only scale dependence of relative effect sizes but also allows for clearer statements about effects being larger in a certain subgroup than in another. The interaction continuum considers three cases: one in which both exposures are causative for the outcome, one in which both are preventive, and one in which one exposure is causative and the other is preventive. Within each case, placement on the interaction continuum arises from the relation of the outcome probability in the doubly exposed group to those in the doubly unexposed and each of the singly exposed groups. The relation of these outcome probabilities can be assessed using either absolute risks or risk ratios. In the case of two exposures that are both causative for the outcome, for high probabilities of the outcome in the doubly exposed group, the interaction may be positive-multiplicative positive-additive and this is the strongest

form of positive interaction in this case on the “interaction continuum”. As the probability of the outcome in the doubly exposed group goes down, it is shown that the form of interaction descends through the ranks of what we will refer to below as: positive-multiplicative positive-additive; no-multiplicative positive-additive, negative-multiplicative positive-additive, negative-multiplicative zero-additive, negative-multiplicative negative-additive, single pure interaction, single qualitative interaction, single-qualitative single-pure interaction, double qualitative interaction, perfect antagonism, inverted interaction. The relations between the two exposures and the outcome will always be constituted by one of these 11 forms on the interaction continuum. Analogous results are also given for settings in which both exposures are protective, or in which one is protective and one is causative; and special cases in which one or both of the main effects of the two exposures is null are also considered. Examples are used to illustrate the interaction continuum in various cases. The primary contribution of this article is conceptual, to attempt to navigate the challenges of claims about larger and smaller effects across different groups in the face of the scale dependence of the relevant effect sizes.

DEFINITIONS AND NOTATION

Let X_1 and X_2 denote two exposures and let Y denote a binary outcome. For simplicity, we will consider the case in which the two exposures are binary. The theory developed in this article will also be applicable to the setting in which the exposures are categorical or continuous with the values of “1” and “0” replaced by some other specific values “ v_1 ” and “ v_0 .” Placement on the interaction continuum may, in that setting, vary with the values of the two exposures that are being compared. Let $p_{ij} = P(Y = 1 | X_1 = i, X_2 = j)$ denote the outcome probability in each of the strata defined by the two exposures. Let $RR_{ij} = P(Y = 1 | X_1 = i, X_2 = j) / P(Y = 1 | X_1 = 0, X_2 = 0)$ denote the risk ratio for the outcome in each of strata defined by the two exposures. The magnitude of additive interaction for risk differences is given by $p_{11} - p_{10} - p_{01} + p_{00}$. The additive interaction is said to be positive if $p_{11} - p_{10} - p_{01} + p_{00} > 0$ and negative if $p_{11} - p_{10} - p_{01} + p_{00} < 0$ and zero if $p_{11} - p_{10} - p_{01} + p_{00} = 0$. Equivalently, the additive interaction is positive if $RR_{11} - RR_{10} - RR_{01} + 1 > 0$, negative if $RR_{11} - RR_{10} - RR_{01} + 1 < 0$ and zero if $RR_{11} - RR_{10} - RR_{01} + 1 = 0$. The quantity $RR_{11} - RR_{10} - RR_{01} + 1$ is sometimes referred to as the “relative excess risk due to interaction” (RERI) or as the “interaction contrast ratio” (ICR).⁴ The magnitude of multiplicative interaction for risk ratios is given by $p_{11}p_{00}/(p_{10}p_{01})$, which can equivalently be rewritten as $RR_{11}/(RR_{10}RR_{01})$. The multiplicative interaction is said to be positive if $RR_{11}/(RR_{10}RR_{01}) > 1$ and negative if $RR_{11}/(RR_{10}RR_{01}) < 1$ and no multiplicative interaction if $RR_{11}/(RR_{10}RR_{01}) = 1$.⁴

We will say that there is a pure interaction for X_1 with respect to X_2 if, in one stratum of X_2 , we have that X_1 has an effect but in the other strata X_1 has no effect, i.e., if we have $p_{10} = p_{00}, p_{11} \neq p_{01}$ or if we have $p_{10} \neq p_{00}, p_{11} = p_{01}$. Likewise, we will say that there is a pure interaction for X_2 with respect to

X_1 if, in one stratum of X_1 , we have that X_2 has an effect but in the other strata X_2 has no effect, i.e., if we have $p_{01} = p_{00}, p_{11} \neq p_{10}$ or $p_{01} \neq p_{00}, p_{11} = p_{10}$. We will say that there is a qualitative interaction for X_1 with respect to X_2 if the effect of X_1 in one stratum of X_2 is in the opposite direction as the effect of X_1 in the other stratum of X_2 , i.e., if we have $p_{10} > p_{00}, p_{11} < p_{01}$ or if we have $p_{10} < p_{00}, p_{11} > p_{01}$. Likewise, we will say that there is a qualitative interaction for X_2 with respect to X_1 if the effect of X_2 in one stratum of X_1 is in the opposite direction as the effect of X_2 in the other stratum of X_1 , i.e., if we have $p_{01} > p_{00}, p_{11} < p_{10}$ or $p_{01} < p_{00}, p_{11} > p_{10}$.

In the language that is used, we will assume that the association between the exposures and the outcome reflect the causal effects of the exposures, or at least that analyses are conditional on some set of measured covariates C that suffice to control for confounding of the effects of both exposures on the outcome.⁴² The assumption that the associations between the exposures and the outcome reflect the causal effects of both exposures is not necessary for the development that follows, but the results will arguably be of greatest interest when the associations of at least one exposure reflects a causal effect.⁴²

INTERACTION CONTINUUM FOR CAUSATIVE EXPOSURES (CASE 1)

We will first consider the case of causative exposures so that both X_1 and X_2 , considered individually in the absence of the other, either increase or leave unchanged the probability of the outcome, i.e., that $p_{10} \geq p_{00}$ and $p_{01} \geq p_{00}$. Placement on the interaction continuum into one of the 11 different forms of interaction then depends on the relative relations of the probability of the outcome in the doubly exposed group, p_{11} , when compared with p_{10}, p_{01} , and p_{00} . To get the 11-fold classification, we will assume that $p_{10} > p_{00}$ and $p_{01} > p_{00}$. If one of p_{10} or p_{01} is equal to p_{00} , then this will be a special case of causative exposures in which one of the main effects is in fact zero, and is discussed in the Appendix. We will also suppose, without loss of generality, that X_1 and X_2 are labeled such that $p_{10} \geq p_{01}$; otherwise one can just change the labels of which exposure constitutes X_1 and which constitutes X_2 .

The 11 forms of interaction on the interaction continuum in this case are documented in Table 1. We will use the term “form of interaction” to refer to sets of outcome probabilities that share certain characteristics (e.g., characteristics described in columns 1, 3, and 4 of Table 1). We will also refer to these as “ranks” but this requires a demonstration of some type of ordering, which we will provide in the text that follows. The ordering concerns the relations as the probability p_{11} varies from larger to smaller values.

If the probability of the outcome in the doubly exposed group is of sufficiently large magnitude so that $p_{11} > p_{10}p_{01}/p_{00}$ then the interaction on both the multiplicative and additive scale will be positive.^{4,24} This is the strongest form of positive interaction for two causative exposures. As the outcome probability p_{11} varies from larger to smaller values, the position

TABLE 1. The Interaction Continuum for Two Causative Exposures

Type Interaction	Rank	Condition on Probabilities ^a	Condition on Risk Ratios ^a
Positive multiplicative positive additive	1	$p_{11} > p_{10}p_{01}/p_{00}$	$RR_{11} > RR_{10}RR_{01}$
No multiplicative positive additive	2	$p_{11} = p_{10}p_{01}/p_{00}$	$RR_{11} = RR_{10}RR_{01}$
Negative multiplicative positive additive	3	$p_{10} + p_{01} - p_{00} < p_{11} < p_{10}p_{01}/p_{00}$	$RR_{10} + RR_{01} - 1 < RR_{11} < RR_{10}RR_{01}$
Negative multiplicative zero additive	4	$p_{11} = p_{10} + p_{01} - p_{00}$	$RR_{11} = RR_{10} + RR_{01} - 1$
Negative multiplicative negative additive	5	$p_{10} < p_{11} < p_{10} + p_{01} - p_{00}$	$RR_{10} < RR_{11} < RR_{10} + RR_{01} - 1$
Single pure interaction for X_2	6	$p_{11} = p_{10}$	$RR_{11} = RR_{10}$
Single qualitative interaction for X_2	7	$p_{01} < p_{11} < p_{10}$	$RR_{01} < RR_{11} < RR_{10}$
Pure interaction for X_1 , qualitative interaction for X_2	8	$p_{11} = p_{01}$	$RR_{11} = RR_{01}$
Double qualitative interaction	9	$p_{00} < p_{11} < p_{01}$	$1 < RR_{11} < RR_{01}$
Perfect antagonism	10	$p_{11} = p_{00}$	$RR_{11} = 1$
Inverted interaction	11	$p_{11} < p_{00}$	$RR_{11} < 1$

^aConditions presuppose that the exposures, X_1 and X_2 , have been labeled so that X_1 has a larger main effect than X_2 .

on the interaction changes and descends through the following ranks. When the outcome probability in the doubly exposed group descends to $p_{11} = p_{10}p_{01}/p_{00}$ then there is no multiplicative interaction but the additive interaction is still positive because $p_{11} - p_{10} - p_{01} + p_{00} = p_{10}p_{01}/p_{00} - p_{10} - p_{01} + p_{00} = (p_{10} - p_{00})(p_{01} - p_{00})/p_{00} > 0$. This is the second form of interaction in the ranking. The third form occurs when we have $p_{11} < p_{10}p_{01}/p_{00}$ but we still have $p_{11} > p_{10} + p_{01} - p_{00}$ in which case we will have a negative multiplicative interaction but a positive additive interaction. When $p_{11} = p_{10} + p_{01} - p_{00}$ exactly, multiplicative interaction will again be negative and the additive interaction will be zero, which is the fourth form in the ranking. When $p_{11} < p_{10} + p_{01} - p_{00}$, then both the additive and the multiplicative interaction will be negative, and this is the fifth form in the ranking and this pertains to all subsequent forms as well. However, when p_{11} is yet smaller further so that $p_{11} = p_{10}$ then we have a pure interaction for X_2 insofar as the effect of X_2 will only be apparent when $X_1 = 0$ since when $X_1 = 1$ then X_2 no longer has an effect as $p_{11} = p_{10}$ and this is the sixth form of interaction. If instead p_{11} is yet smaller so that we have $p_{11} < p_{10}$, but $p_{11} > p_{01}$ then we have a qualitative interaction for X_2 with respect to X_1 since $p_{01} > p_{00}$ but $p_{11} < p_{10}$ and this is the seventh form of interaction, and the qualitative interaction for X_2 likewise pertains to all subsequent forms of interaction.

When p_{11} is yet smaller so that $p_{11} = p_{01}$, then we still have a qualitative interaction for X_2 but now also a pure interaction for X_1 since $p_{10} > p_{00}$ but $p_{11} = p_{01}$, which is the eighth form of interaction. When $p_{11} < p_{01}$ but we still have $p_{11} > p_{00}$ then we have a qualitative interaction for X_2 but now also a qualitative interaction for X_1 since $p_{10} > p_{00}$ but $p_{11} < p_{01}$ and this is our ninth form of interaction; the qualitative interactions for X_1 and X_2 likewise pertain to both of the final two forms of interaction. When $p_{11} = p_{00}$ we will refer to this as “perfect antagonism” because each of X_1 and X_2 , considered separately, have a causative effect on the outcome, but when both are present together the risk of the outcome is exactly what it is without either exposure, and this is our tenth form

of interaction. Finally, if $p_{11} < p_{00}$ we will refer to this as an “inverted interaction” since each of X_1 and X_2 , considered separately, have a causative effect on the outcome, but when both are present together the risk of the outcome is in fact even lower than when neither exposure is present, and this is our 11th form of interaction.

One can thus place a particular set of outcome probabilities into one of these 11 states on the interaction continuum. All of these conditions can also be re-expressed in terms of risk ratios as well, as given in Table 1. A numerical example of how the rank of an interaction on the interaction continuum varies with p_{11} is given in the Figure for the setting in which $p_{00} = 0.1, p_{01} = 0.2, p_{10} = 0.4$.

Note that it is only for the first form of interaction (positive multiplicative, positive additive) that we can unambiguously say (on both the risk difference and the risk ratio scales) that the effect of one exposure is greater in one stratum than the other; it is greater on both the additive and on the multiplicative scale. For the third form of interaction, it is larger on the additive and smaller on the multiplicative, and here we must be especially cautious with regard to statements about the relative magnitude of the effect, since it is very clearly scale dependent. For the fifth and all subsequent forms of interaction, the effect is smaller on both the multiplicative and on the additive scales; but for the seventh form of interaction onwards, the direction of the effect for the second exposure actually reverses, and for the ninth form of interaction onwards, the direction of the effects for both the first and the second exposure reverses. Once again, whether an “effect” is larger in one subgroup versus another is scale dependent. It is only unambiguously “larger” in the first form of interaction and only unambiguously “smaller” in the fifth and all subsequent forms of interaction. Moreover, even with rank 1, or ranks 5 and above, on the interaction continuum, the effect is only necessarily unambiguously “larger” or “smaller” on the risk difference scale and the risk ratio scale. It is still possible that the comparison of the magnitude of the effects reverses

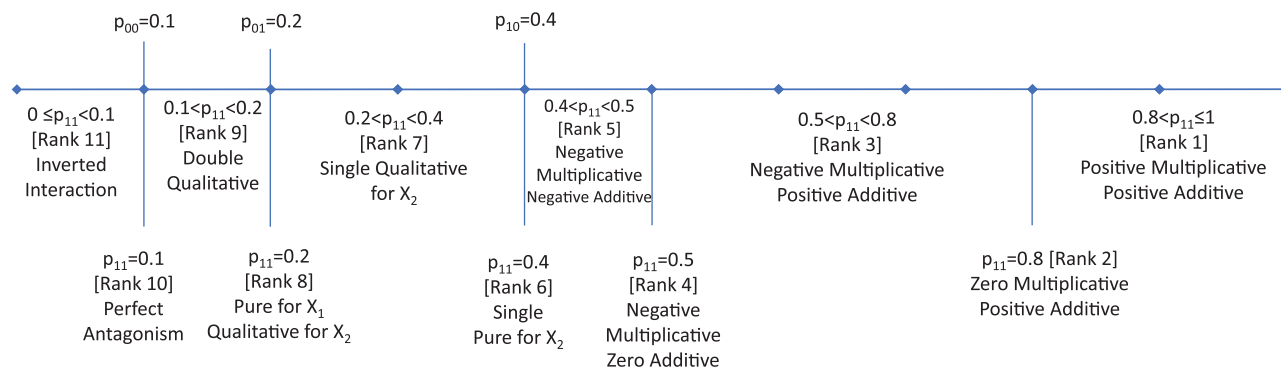


FIGURE. The interaction continuum (example with $p_{00} = 0.1$, $p_{01} = 0.2$, $p_{10} = 0.4$).

on other more obscure scales.³⁷ However, the risk difference and risk ratio scales are arguably the most relevant for epidemiology and so a characterization of the relative magnitude of the effects across these two scales, as provided by the proposed interaction continuum, may often be of some use.

Note also that the categories that make up the interaction continuum are mutually exclusive and collectively exhaustive. This can be seen from the third column of Table 1: the outcome probability p_{11} must lie in one of the categories presented in the third column. In some cases, however, with outcomes that are more common, the highest ranks on the interaction continuum may not be obtainable for a given set of outcomes probabilities p_{00} , p_{01} , and p_{10} ; e.g., with $p_{00} = 0.1$, $p_{01} = 0.3$, $p_{10} = 0.5$, it is not possible to have a positive multiplicative interaction; the multiplicative interaction for risk ratios will always be negative regardless of p_{11} ; it is still possible to have a positive additive interaction if $p_{11} > 0.9$ so the highest rank on the interaction continuum that would be possible here would be the third rank. We will now illustrate the interaction continuum with a series of examples.

EXAMPLES OF THE INTERACTION CONTINUUM WITH CAUSATIVE EXPOSURES

In this section, we will illustrate different states of the interaction continuum with examples from the epidemiologic literature. The examples in this section should be considered as illustrations only; they are not definitive claims about the nature of the interaction in any of these examples. We will not be considering sampling variability in these examples, and will simply use the risk ratio estimates to illustrate possible cases. Further remarks on issues of sampling variability will be given at the conclusion of the article.

Bhavnani et al.⁴³ considered possible interaction between the rotavirus and giardia pathogens in diarrheal disease and report the risk ratios in Table 2. Here $RR_{11} = 10.7 > 2.9 = (2.6)(1.1) = RR_{10}RR_{01}$ and thus this is an instance of positive multiplicative and positive additive interaction, the strongest form (Rank 1) of positive interaction in the hierarchy.

Brown and Harris⁴⁴ considered possible interaction between stressful adverse events and lack of intimacy in their

TABLE 2. Associations (RR's)⁴³ of Diarrheal Disease with Giardia (X_1) and Rotavirus (X_2): Positive Multiplicative, Positive Additive (Rank 1)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	1.1	1.1
$X_1 = 1$	2.6	10.7	4.1

TABLE 3. Associations (RR's)⁴⁴ of Depression with Stress (X_1) and Lack of Intimacy (X_2): No Multiplicative, Positive Additive (Rank 2)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	3.2	3.2
$X_1 = 1$	10.2	32	3.2

TABLE 4. Associations (RR's)⁴⁵ of Lung Cancer with Smoking (X_1) and Asbestos (X_2): Negative Multiplicative, Positive Additive (Rank 3)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	6.1	6.1
$X_1 = 1$	8.6	40.9	4.8

associations with depression; approximate risk ratios are reported in Table 3. Here to a close approximation there is no multiplicative interaction since $RR_{11}/(RR_{10}RR_{01}) = 32/(10.2 \times 3.2) \approx 1$ but there is strong additive interaction since $RR_{11} - RR_{10} - RR_{01} + 1 = 32 - 10.2 - 3.2 + 1 = 19.6 > 0$. This is the second form of interaction in the continuum.

Hilt et al.⁴⁵ considered possible interaction between smoking and asbestos in their associations with lung cancer; risk ratios are reported in Table 4. Here we have a positive additive interaction since $RR_{11} - RR_{10} - RR_{01} + 1 = 27.2 > 0$, but negative multiplicative interaction since $RR_{11}/(RR_{10}RR_{01}) = 40.9/(8.6 \times 6.1) = 0.78 < 1$. The actual risks reported in Hilt et al. are $p_{00} = 0.0011$, $p_{10} = 0.0095$, $p_{01} = 0.0067$, $p_{11} = 0.0450$. Note that on the risk difference scale, the effect of asbestos

exposure is larger for smokers than for nonsmokers because the effect for smokers is $p_{11} - p_{10} = 0.0450 - 0.0095 = 0.0355$ and for nonsmokers is only $p_{01} - p_{00} = 0.0067 - 0.0011 = 0.0056$. However, on the risk ratio scale, the effect of asbestos exposure is smaller for smokers than for nonsmokers because the effect for smokers is $p_{11}/p_{10} = 0.0450/0.0095 = 4.7$ and but for $p_{01}/p_{00} = 0.0067/0.0011 = 6.1$. This is an example of the third form of interaction in the continuum. Again, which effect is “larger” is dependent on the scale.

Stern et al.⁴⁶ consider possible interaction between methionine variants at XRCC3 codon 241 (denoted by X_1) the Arg/Arg genotype for XRCC1 codon 194 (denoted by X_2) in their associations with bladder cancer; approximate risk ratios are reported in Table 5. Here we have negative multiplicative interaction because $RR_{11}/(RR_{10}RR_{01}) = 4.0/(3.3 \times 3.2) = 0.38 < 1$ and negative additive interaction because $RR_{11} - RR_{10} - RR_{01} + 1 = 4.0 - 3.3 - 3.2 + 1 = -1.5 < 0$. The effect of the Arg/Arg genotype for XRCC1 on bladder cancer is smaller when methionine variants at XRCC3 are present for both risk ratios and risk differences. This is an example of the fifth form of interaction in the continuum.

Paunio et al.⁴⁷ consider possible interaction between older age (age 46+ years) and alcohol consumption in their associations with *Helicobacter pylori* infection; their approximate unadjusted risk ratios are reported in Table 6. This is an example of a single qualitative interaction (Rank 7 in the continuum), specifically here for alcohol consumption because alcohol consumption (X_2) is causative for younger individuals (i.e., when $X_1 = 0$) but preventive for older individuals (i.e., when $X_1 = 1$).

Stern et al.⁴⁸ consider possible interaction between smoking and the Gln/Gln genotype for XPD codon 751 in their associations with bladder cancer; approximate risk ratios are reported in Table 7. This is an example of a double-qualitative interaction (Rank 9 in the continuum) because the effect of X_1 is causative when X_2 is absent but preventive when X_2 is present and likewise the effect of X_2 is causative when X_1 is absent but preventive when X_1 is present.

TABLE 5. Associations (RR's)⁴⁶ of Bladder Cancer with XRCC3 variants (X_1) and XRCC1 variants (X_2): Negative Multiplicative, Negative Additive (Rank 5)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	3.2	3.2
$X_1 = 1$	3.3	4.0	1.2

TABLE 6. Associations (RR's)⁴⁷ of *Helicobacter pylori* infection with Older Age (X_1) and Alcohol Consumption (X_2): Single Qualitative Interaction for X_2 (Rank 7)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	2.4	2.4
$X_1 = 1$	7.6	5.2	0.68

INTERACTION CONTINUUM FOR PREVENTIVE EXPOSURES (CASE 2)

We will now consider the case of preventive exposures so that both X_1 and X_2 , considered individually in the absence of the other, either decrease or leave unchanged the probability of the outcome, i.e., the case that $p_{10} \leq p_{00}$ and $p_{01} \leq p_{00}$. Placement on the interaction continuum into one of the 11 different forms of interaction again depends on the relative relations of the probability of the outcome in the doubly exposed group, p_{11} , when compared with p_{10} , p_{01} , and p_{00} . To get the 11-fold classification, we will assume that $p_{10} < p_{00}$ and $p_{01} < p_{00}$. If one of the p_{10} or p_{01} is equal to p_{00} , then this will be a special case, discussed in the Appendix, of preventive exposures in which one of the main effects is in fact zero. We will also suppose, without loss of generality, that X_1 and X_2 are labeled such that $p_{10} \leq p_{01}$.

The 11 forms of interaction on the interaction continuum for preventive exposures are documented in Table 8. If the probability of the outcome in the doubly exposed group is sufficiently small so that $p_{11} < p_{10} + p_{01} - p_{00}$, then the interaction will be negative on both the multiplicative and additive scales. This is the strongest form of negative interaction for two preventive exposures. In this case, each exposure amplifies the protective effects of the other on either the additive or the multiplicative scale. As the outcome probability p_{11} varies from smaller to larger values, the position on the interaction changes and moves through the following ranks.

When the outcome probability in the doubly exposed group rises to $p_{11} = p_{10} + p_{01} - p_{00}$, then the additive interaction is zero but the multiplicative interaction is still negative because

$$\begin{aligned} p_{11}p_{00}/(p_{10}p_{01}) &= p_{11}p_{00}/\{[p_{00}+(p_{10}-p_{00})]\{p_{00}+(p_{01}-p_{00})\}\} \\ &= p_{11}p_{00}/\{[p_{00}+(p_{10}-p_{00})+(p_{01}-p_{00})]p_{00}+(p_{10}-p_{00})(p_{01}-p_{00})\} \\ &= p_{11}p_{00}/[p_{11}p_{00}+(p_{10}-p_{00})(p_{01}-p_{00})] \leq 1 \end{aligned}$$

Then this is the second form of interaction in the ranking. The third form occurs when $p_{11} > p_{10} + p_{01} - p_{00}$ but we still have $p_{11} < p_{10}p_{01}/p_{00}$ in which case we will have a negative multiplicative interaction but a positive additive interaction.

When $p_{11} = p_{10}p_{01}/p_{00}$ exactly, there will again be positive additive interaction but no multiplicative interaction,

TABLE 7. Associations (RR's)⁴⁸ of Bladder Cancer with smoking (X_1) and XPD codon 751 genotype (X_2): Double Qualitative Interaction (Rank 9)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	2.6	2.6
$X_1 = 1$	3.6	2.1	0.6

TABLE 8. The Interaction Continuum for Two Preventive Exposures

Type Interaction	Rank	Condition on Probabilities	Condition on Risk Ratios
Negative multiplicative negative additive	1	$p_{11} < p_{10} + p_{01} - p_{00}$	$RR_{11} < RR_{10} + RR_{01} - 1$
Negative multiplicative zero additive	2	$p_{11} = p_{10} + p_{01} - p_{00}$	$RR_{11} = RR_{10} + RR_{01} - 1$
Negative multiplicative positive additive	3	$p_{10} + p_{01} - p_{00} < p_{11} < p_{10}p_{01}/p_{00}$	$RR_{10} + RR_{01} - 1 < RR_{11} < RR_{10}RR_{01}$
No multiplicative positive additive	4	$p_{11} = p_{10}p_{01}/p_{00}$	$RR_{11} = RR_{10}RR_{01}$
Positive multiplicative positive additive	5	$p_{10}p_{01}/p_{00} < p_{11} < p_{10}$	$RR_{10}RR_{01} < RR_{11} < RR_{10}$
Single pure interaction for X_2	6	$p_{11} = p_{10}$	$RR_{11} = RR_{10}$
Single qualitative interaction for X_2	7	$p_{10} < p_{11} < p_{01}$	$RR_{10} < RR_{11} < RR_{01}$
Pure interaction for X_1 , qualitative interaction for X_2	8	$p_{11} = p_{01}$	$RR_{11} = RR_{01}$
Double qualitative interaction	9	$p_{01} < p_{11} < p_{00}$	$RR_{01} < RR_{11} < RR_{00}$
Perfect antagonism	10	$p_{11} = p_{00}$	$RR_{11} = RR_{00}$
Inverted interaction	11	$p_{11} > p_{00}$	$RR_{11} > RR_{00}$

*Conditions presuppose that the exposures, X_1 and X_2 , have been labeled so that X_1 has a larger preventive main effect than X_2 .

TABLE 9. Associations (RR's)⁴⁹ of Suicide with Service Attendance (X_1) and Catholic Affiliation (X_2): Positive Multiplicative, Positive Additive (Rank 1)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	0.97	0.97
$X_1 = 1$	0.34	0.05	0.15

which is the fourth form in the ranking. When $p_{11} > p_{10}p_{01}/p_{00}$, then both the additive and the multiplicative interaction will be positive, and this is the fifth form in the ranking and this pertains to all subsequent forms as well. However, when p_{11} is yet larger so that $p_{11} = p_{10}$, then we have a pure interaction for X_2 insofar as the effect of X_2 will only be apparent when $X_1 = 0$ because when $X_1 = 1$ then X_2 no longer has an effect as $p_{11} = p_{10}$ and this is the sixth form of interaction. If instead we have $p_{11} > p_{10}$, but $p_{11} < p_{01}$ then we have a qualitative interaction for X_2 with respect to X_1 since $p_{01} < p_{00}$ but $p_{11} > p_{10}$ and this is the seventh form of interaction, and the qualitative interaction for X_2 likewise pertains to all subsequent forms of interaction.

When p_{11} is yet further larger so that $p_{11} = p_{01}$, then we still have a qualitative interaction for X_2 but now also a pure interaction for X_1 since $p_{10} < p_{00}$ but $p_{11} = p_{01}$, which is the eighth form of interaction. When $p_{11} > p_{01}$ but we still have $p_{11} < p_{00}$ then we have a qualitative interaction for X_2 but now also a qualitative interaction for X_1 since $p_{10} < p_{00}$ but $p_{11} > p_{01}$ and this is our ninth form of interaction; the qualitative interactions for X_1 and X_2 likewise pertain to both of the final two forms of interaction.

When $p_{11} = p_{00}$, we will refer to this as “perfect antagonism” because each of X_1 and X_2 , considered separately, have a preventive effect on the outcome, but when both are present together the risk of the outcome is exactly what it is without either exposure, and this is our tenth form of interaction. Finally, if $p_{11} > p_{00}$ we will refer to this as an “inverted interaction” since each of X_1 and X_2 , considered separately, have a preventive effect on

the outcome, but when both are present together the risk of the outcome is in fact even higher than when neither exposure is present, and this is our 11th form of interaction.

One can thus place a particular set of outcome probabilities into one of these 11 states on the interaction continuum for preventive exposures. All of these conditions can also be re-expressed in terms of risk ratios as well, as given in Table 8.

Note that it is only for the first form of interaction (negative multiplicative, negative additive) that we can unambiguously say that the effect of one exposure is more protective in one stratum than the other; it is greater (i.e., more negative, more protective) on both the additive and on the multiplicative scale. For the third form of interaction, the protective effect is more substantial on the multiplicative scale, but less substantial on the additive scale, and here we must be especially cautious with regard to statements about the relative magnitude of the effect, since it is very clearly scale dependent. Note that while for causative exposures, as the outcome probability p_{11} decreases, one first loses the positive multiplicative and then the positive additive, it is the reverse for preventive exposures: as the outcome probability p_{11} increases one first loses the negative additive and then the negative multiplicative interaction.

We will briefly illustrate the results with two examples. VanderWeele et al.⁴⁹ considered potential interaction between religious service attendance and Catholic versus Protestant affiliation in their associations with completed suicide; approximate risk ratios are given in Table 9. Here, $RR_{11} - RR_{10} - RR_{01} + 1 = 0.05 - 0.34 - 0.97 + 1 = -0.26 < 0$ and we would have here both negative additive and negative multiplicative interaction, which is the strongest form of interaction (Rank 1) for preventive effects. The estimated protective effects of service attendance appeared to be more substantial for Catholics than for Protestants on both the risk ratio and the risk difference scale. Knol et al.⁵⁰ considered potential interaction between the use of angiotensin-converting-enzyme (ACE) inhibitors and the presence of the DD genotype on the ACE gene in their associations with diabetes; approximate risk ratios are given

in Table 10. Here $(RR_{10} = 0.7) < (RR_{11} = 0.86) < (RR_{01} = 0.90)$ and so the interaction is the seventh on the interaction continuum for preventive exposures: we have positive multiplicative and additive interaction (each exposure is less protective in the presence of the other on both the risk ratio and risk difference scale) and moreover there is a qualitative interaction for the DD genotype in which it is protective when ACE inhibitors are absent, but causative when ACE inhibitors are present.

INTERACTION CONTINUUM FOR MIXED EXPOSURES (CASE 3)

We will now consider the setting in which, when considered singly, one of the exposures is causative and the other is protective. Without loss of generality, we will assume that X_1 and X_2 are labeled such that $p_{10} > p_{00}$ and $p_{01} < p_{00}$; otherwise one can just change the labels of which exposure constitutes X_1 and which constitutes X_2 . If one of the probabilities p_{10} or p_{01} is equal to p_{00} , then this is just a special case of either the setting for two causative or two preventive exposures above.

The forms of interaction on the interaction continuum in this case are documented in Table 11. If the probability of the outcome in the doubly exposed group is of sufficiently large magnitude so that $p_{11} > p_{10}$ then the interaction on both the multiplicative and additive scale will be positive and moreover there will be a qualitative interaction for X_2 because the effect of X_2 when X_1 is absent will be protective $p_{01} - p_{00} < 0$ but when X_1 is present it will be causative $p_{11} - p_{10} > 0$. This is the strongest form of positive interaction for two mixed exposures.

TABLE 10. Associations (RR's)⁵⁰ of Diabetes with ACE Inhibitor (X_1) and DD genotype (X_2): Single Qualitative Interaction for X_2 (Rank 7)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR's
$X_1 = 0$	1	0.90	0.90
$X_1 = 1$	0.70	0.86	1.2

As the outcome probability p_{11} varies from larger to smaller values, the position on the interaction changes and descends through the following ranks. When the outcome probability in the doubly exposed group descends to $p_{11} = p_{10}$, then we will again have positive multiplicative and additive interactions but now we will have a pure interaction for X_2 rather than a qualitative interaction for X_2 and this is the second form of interaction in this case. When $p_{11} < p_{10}$ but it is still the case that $p_{11} > p_{10} + p_{01} - p_{00}$, then we no longer have pure or qualitative interaction for X_2 but we do still have positive multiplicative and positive additive interaction, and this is the third form in the continuum. When $p_{11} = p_{10} + p_{01} - p_{00}$, we will have zero additive interaction but we will still have positive multiplicative interaction since

$$\begin{aligned}
 p_{11}p_{00}/(p_{10}p_{01}) &= p_{11}p_{00}/\{[p_{00} + (p_{10} - p_{00})]\{p_{00} + (p_{01} - p_{00})\}\} \\
 &= p_{11}p_{00}/\{[p_{00} + (p_{10} - p_{00}) + (p_{01} - p_{00})]p_{00} + (p_{10} - p_{00})(p_{01} - p_{00})\} \\
 &= p_{11}p_{00}/[p_{11}p_{00} + (p_{10} - p_{00})(p_{01} - p_{00})] \geq 1,
 \end{aligned}$$

which is the fourth form in the ranking.

When $p_{11} < p_{10} + p_{01} - p_{00}$ but $p_{11} > p_{10}p_{01}/p_{00}$, then we will have negative additive but positive multiplicative, which is the fifth form. When p_{11} descends yet further to $p_{11} = p_{10}p_{01}/p_{00}$, then we will have no multiplicative and negative additive interaction, which is the sixth form. If instead we have $p_{11} < p_{10}p_{01}/p_{00}$ but $p_{11} > p_{01}$, then we will have negative multiplicative and negative additive interaction, and this is the seventh form; the negative multiplicative and negative additive also pertains to the final two forms of interaction in this case.

If p_{11} descends yet further to $p_{11} = p_{01}$, then we have a pure interaction for X_1 since $p_{10} > p_{00}$ but $p_{11} = p_{01}$ and this is the eighth form. And if p_{11} descends yet further so that $p_{11} < p_{01}$, then we have a qualitative interaction for X_1 since $p_{10} > p_{00}$ but $p_{11} < p_{01}$ and this is the ninth form in the ranking of

TABLE 11. The Interaction Continuum for One Causative and One Preventive Exposure

Type Interaction	Rank	Condition on Probabilities ^a	Condition on Risk Ratios ^a
Positive multiplicative positive additive, qualitative interaction for X_2	1	$p_{11} > p_{10}$	$RR_{11} > RR_{10}$
Positive multiplicative positive additive, pure interaction for X_2	2	$p_{11} = p_{10}$	$RR_{11} = RR_{10}$
Positive multiplicative positive additive	3	$p_{10} + p_{01} - p_{00} < p_{11} < p_{10}$	$RR_{10} + RR_{01} - RR_{00} < RR_{11} < RR_{10}$
Positive multiplicative zero additive	4	$p_{11} = p_{10} + p_{01} - p_{00}$	$RR_{11} = RR_{10} + RR_{01} - RR_{00}$
Positive multiplicative negative additive	5	$p_{10}p_{01}/p_{00} < p_{11} < p_{10} + p_{01} - p_{00}$	$RR_{10}RR_{01} < RR_{11} < RR_{10} + RR_{01} - RR_{00}$
No multiplicative negative additive	6	$p_{11} = p_{10}p_{01}/p_{00}$	$RR_{11} = RR_{10}RR_{01}$
Negative multiplicative negative additive	7	$p_{01} < p_{11} < p_{10}p_{01}/p_{00}$	$RR_{01} < RR_{11} < RR_{10}RR_{01}$
Negative multiplicative negative additive, pure interaction for X_1	8	$p_{11} = p_{01}$	$RR_{11} = RR_{01}$
Negative multiplicative negative additive, qualitative interaction for X_1	9	$p_{11} < p_{01}$	$RR_{11} < RR_{01}$

^aConditions presuppose that the exposures, X_1 and X_2 , have been labeled so that X_1 has causative main effect and X_2 a preventive main effect.

the interaction continuum in this case. In this setting of one causative and one preventive exposure, we might still say that “perfect antagonism” occurs when $p_{11} = p_{00}$ so that the causative effect of X_1 and the preventive effect of X_2 cancel each other perfectly when both are present. However, depending on the specific outcome probabilities p_{10} , p_{01} , and p_{00} , this “perfect antagonism” can occur in any of the ranks from 3 to 7 of the interaction continuum hierarchy in this case. Also in this setting of one causative and one preventive exposure, there is no analogue to an “inverted interaction” as with cases 1 and 2 with two causative or two preventive exposures, because if one exposure is causative and the other is preventive, then the effect of having both exposures will either be in the same direction of the first exposure (causative) or the second (preventive) or neutral; it cannot be in the opposite direction of both of the exposures as with inverted interactions in Cases 1 and 2.

We will briefly illustrate the results with two examples. Aschiero et al.⁵¹ reported associations between coffee consumption (6+ cups/day vs. 0 cups) and Parkinson’s disease stratified by gender; approximate unadjusted risk ratios are given in Table 12. Here we have $RR_{01} < RR_{11} < RR_{10}$ and thus this is an instance of Rank 7 in the interaction continuum for this case; we have a negative multiplicative and negative additive interaction, but no qualitative interaction.

Li et al.⁵² considered possible interaction between Catholic versus Protestant affiliation and religious service attendance in the associations with divorce; approximate risk ratios are given in Table 13. Here, we have $p_{11} < p_{01}$ and thus this is an instance of Rank 9 in the interaction continuum for this case; we have a negative multiplicative and negative additive interaction and in fact a qualitative interaction for X_1 . While Catholic versus Protestant affiliation in the absence of service attendance increases risk of divorce, Catholic versus Protestant affiliation in the presence of service attendance decreases the risk of divorce (qualitative interaction), and in this case the protective effect of attendance is more substantial for

Catholics than it is for Protestants on both risk difference and risk ratio scales (negative interaction).

DISCUSSION

The results here allow investigators to categorize interaction on a continuum. Doing so clarifies the types of claims that can be made concerning when an effect of an exposure is “larger” or “smaller” in one subgroup defined by a second exposure versus another, while also acknowledging the scale dependence of these claims. Only in certain circumstances, can claims be made about “larger” or “smaller” effects that are equally applicable to both risk ratio and risk difference scales, but placement of a set of outcome probabilities on this interaction continuum can make clear whether such statements are justified, and if not, then what other claims about interaction can be made. The ranking on the interaction continuum can help provide some understanding of the dynamics of the two exposures in their relation to the outcome and we have illustrated this through a number of examples.

The proposal of potentially reporting results on this interaction continuum is in no way intended to replace more specific, and arguably often more relevant and useful, motivations for assessing interaction such as gaining insights relevant for targeting subgroups to maximize public health impact when resources are constrained,^{1–7} determining optimal treatment assignments even when resources are not constrained,^{8–16} evaluating mechanisms,^{4–6,17–26} identifying effect modifiers to eliminate exposure effects,^{5,6,27,28} and assessing generalizability.^{29–36} Careful thought should always be given to why an interaction analysis is being carried out. And with these more specific questions, often results of an interaction analysis on a particular scale is in fact what gives the relevant information.^{3–6} Moreover, often these other motivations are of greater scientific and policy relevance than is simply trying to answer the question “whether the effect is larger in one group versus another” and how this might vary across scales.

Of course this latter question, addressed by the interaction continuum, is not entirely unrelated to the more specific scientific and policy-relevant questions. Placement on the interaction continuum contains some, but not all, implications for addressing these various other motivations. Knowing about qualitative interaction, for example, is extremely important substantively as it indicates that some individuals should be treated but others not, even if resources are unconstrained.^{8–12} Additive interaction is important in that it indicates whether one group or another should be treated if resources are constrained.^{3–6} Positive additive interaction is also related in certain cases to sufficient cause interaction in evaluating mechanisms.^{19–26} Some of these more specific questions are thus also indirectly addressed by the interaction continuum, but not all, and so again the motivations for assessing interaction should be considered carefully, and alternative or additional interaction analyses may be useful.

TABLE 12. Associations (RR’s)51 of Parkinson’s Disease with Male Gender (X_1) and Coffee Consumption (X_2): Negative Multiplicative, Negative Additive (Rank 7)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR’s
$X_1 = 0$	1	0.58	0.58
$X_1 = 1$	2.4	0.89	0.37

Table 13. Associations (RR’s)52 of Suicide with Catholic Affiliation (X_1) and Service Attendance (X_2): Negative Multiplicative, Negative Additive, Qualitative Interaction for X_1 (Rank 9)

	$X_2 = 0$	$X_2 = 1$	Stratum-Specific RR’s
$X_1 = 0$	1	0.67	0.67
$X_1 = 1$	1.24	0.60	0.48

Even when the limited question of “whether the effect is larger in one group versus another” is what is of interest, the interaction continuum helps make clear, what has been repeatedly emphasized previously,^{1–6,33–38} that the answer to this question is scale dependent. This point, however, is still repeatedly neglected in reporting practices of interaction,⁴¹ and it is hoped that by reporting interactions on the interaction continuum this important issue will become more transparent and evident in the reporting practices of interaction analyses in articles.

Placement on the interaction continuum is not invariant to the recoding of the exposure or the outcome. This is the case with many forms of interaction.^{4–6,23,37,50} With the interaction continuum, a recoding of one of the exposures would, for example, move the outcome probabilities from Case 1 above to Case 3 above. There are of course various relations concerning the placement of the outcome probabilities on the interaction continuum across various recodings of the exposure and/or outcome. However, a full mapping of these would require a paper of near equal length to the present one.

A perhaps more difficult challenge with the implementation of this interaction continuum scheme in practice concerns handling sampling variability. We have effectively assumed that outcome probabilities are known. In practice, they are estimated and there can be considerable uncertainty with regard to their actual values or relative orderings. In the context of very large sample sizes and narrow confidence intervals, it may be possible to categorize a particular set of outcome probabilities in one of the 11 ranks of Tables 1 or 8 or 11, for example, even without exact knowledge of the true probabilities. However, in many other cases, the uncertainty in the outcome probability estimates and in their relative ordering may make such classification uncertain. If the outcome probability in one of the singly exposed groups is very close to that of the doubly unexposed group, it may even be difficult to discern whether Case 1, 2, or 3 above is the relevant interaction continuum on which to place the outcomes probabilities. In these cases, inferential procedures would need to be developed to characterize the uncertainty as to where a particular set of outcome probability estimates falls in the interaction continuum; this is not a trivial task.

One, only partially satisfactory, possibility might be to assign uniform priors on the outcome probabilities and then use Bayesian statistics to obtain posterior probabilities that the outcomes probabilities lie in each rank of the relevant interaction continuum. However, the even-numbered ranks (ranks 2, 4, 6, 8, and 10) on Tables 1, 8, and 11 constitute exact probability equalities and unless a point mass were given for these in the prior, the posterior estimates for these ranks would remain 0. This also corresponds to the fact that it is difficult to definitively establish an exact equality with data. Instances arose in our examples as well: in Table 3, it is difficult to discern whether there is no multiplicative interaction, or perhaps a slightly negative one.

Nevertheless, in certain circumstances the posterior probability may be exceptionally high in one of the odd-numbered ranks, which constitute four-dimensional outcome probability regions and it may then be reasonable to conclude that a particular set of outcome probabilities occupies a specific rank in the interaction continuum. In other cases, it may be that the majority of the posterior probability distribution occupies two adjacent odd-numbered ranks and the intervening even-numbered rank, e.g., ranks 7, 8, 9 in Table 1, so that one could conclude negative multiplicative interaction, negative additive interaction, and a qualitative interaction for X_2 , even though there would still be uncertainty whether there were also a pure or qualitative interaction for X_1 .

Further development of statistical inference in evaluating placement on the interaction continuum would be desirable. However, the contribution of this article was intended to be conceptual: to clarify, with a set of known outcome probabilities, what statements about “larger” and “smaller” effects can be made while acknowledging scale dependence and to rank the types of interactions according to the relations between the outcome probability in the doubly exposed group compared with the others.

APPENDIX

Special Degenerate Cases of the Interaction Continuum

In the discussion above, we considered settings in which, when considered singly, (1) both exposures were causative, or (2) both exposures were preventive, or (3) one exposure was causative and the other preventive. We noted that there are special cases in which one exposure might have no effect in the absence of the other. In these settings, the interaction continuum presented above for the various cases is still applicable but collapses to a lesser number of ranked categories.

Consider Case 1 of causative exposures in which the second exposure in fact has no effect in the absence of the first so that $p_{10} > p_{00}$ but $p_{01} = p_{00}$. In this setting, there will be a pure interaction for exposure X_2 . The interaction continuum hierarchy in Table 1 is still applicable for rank 1 and constitutes positive additive and positive multiplicative interaction; however, after that, ranks 2–6 all collapse to the single condition $p_{11} = p_{10}$, which is no multiplicative interaction, zero additive interaction, and in fact no effect for X_2 whatsoever since $p_{01} = p_{00}$ and $p_{11} = p_{10}$. Rank 7 remains and constitutes negative multiplicative interaction, negative additive interaction, with a preventive effect for X_2 in the presence of X_1 . Ranks 8–10 collapse to the condition $p_{11} = p_{00} = p_{01}$ and indicate a pure interaction for X_1 as well, and Rank 11 remains and indicates a qualitative interaction for X_1 . There are thus effectively only five separate ranks in the interaction hierarchy in this case, which we might call as the following: (1) positive interaction, (2) zero interaction, (3) negative interaction, (4) pure interaction for X_1 , and (5) qualitative interaction for X_1 .

In all of these ranks, there is either a pure interaction for X_2 or no effect for X_2 at all.

Likewise, consider Case 2 of preventive exposures in which the second exposure in fact has no effect in the absence of the first so that $p_{10} < p_{00}$ but $p_{01} = p_{00}$. In this setting, there will again be a pure interaction for exposure X_2 . The interaction continuum hierarchy in Table 8 is still applicable for rank 1; however, after that, ranks 2–6 all collapse to the single condition $p_{11} = p_{10}$, which is no multiplicative interaction, zero additive interaction, and in fact no effect for X_2 whatsoever since $p_{01} = p_{00}$ and $p_{11} = p_{10}$. Rank 7 remains and constitutes positive multiplicative interaction, positive additive interaction, with a causative effect for X_2 in the presence of X_1 . Ranks 8–10 collapse to the condition $p_{11} = p_{00} = p_{01}$ and indicates a pure interaction for X_1 as well, and Rank 11 remains and indicates a qualitative interaction for X_1 . There are thus effectively only five separate ranks in the interaction hierarchy in this case, which we might call as the following: (1) negative interaction, (2) zero interaction, (3) positive interaction, (4) pure interaction for X_1 , and (5) qualitative interaction for X_1 .

Finally, it is possible that neither exposure has an effect in the absence of the other so that $p_{10} = p_{01} = p_{00}$. In this case, the only relevant distinctions are as follows: (1) $p_{11} > p_{10} = p_{01} = p_{00}$, which is a positive interaction on all scales and a double pure interaction; (2) $p_{11} = p_{10} = p_{01} = p_{00}$, which is no effect of either exposure; and (3) $p_{11} < p_{10} = p_{01} = p_{00}$, which is a negative interaction on all scales and a double pure interaction.

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