Sufficient cause interactions for categorical and ordinal exposures with three levels

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SUMMARY

Definitions are given for weak and strong sufficient cause interactions in settings in which the outcome is binary and in which there are two exposures of interest that are categorical or ordinal. Weak sufficient cause interactions concern cases in which a mechanism will operate under certain values of the two exposures but not when one or the other of the exposures takes some other value. Strong sufficient cause interactions concern cases in which a mechanism will operate under certain values of the two exposures but not when one or the other of the exposures takes any other value. Empirical conditions are derived for such interactions when exposures have two or three levels and are related to regression coefficients in linear and log-linear models. When the exposures are binary, the notions of a weak and a strong sufficient cause interaction coincide, but not when the exposures are categorical or ordinal. The results are applied to examples concerning gene-gene and gene-environment interactions.

Some key words: Categorical data; Gene-environment; Interaction; Sufficient cause; Synergism.

1. INTRODUCTION

The sufficient cause framework conceptualizes causation as a collection of causal mechanisms, each requiring component causes to operate. These mechanisms are called sufficient causes as each is sufficient to bring about the outcome. This framework was made popular in the epidemiological literature by Rothman (1976). His work was preceded by similar descriptions in the philosophical (Mackie, 1965) and epidemiological (MacMahon & Pugh, 1967) literatures, and a very crude sufficient cause model appears in Cayley (1853).

This framework allows for the analysis of certain types of mechanistic interaction (VanderWeele & Robins, 2007, 2008; VanderWeele, 2009). In particular, when two causes are both required for a particular mechanism to operate, then synergism is said to be present. VanderWeele & Robins (2008) gave empirical conditions to test for synergism between two or three binary variables. In some potential applications, however, the exposures of interest are not binary; for example, genetic exposures are often coded as ternary variables whose levels indicate 0, 1 or 2 variant alleles. This paper considers empirical tests for synergism when one or both exposures are polytomous, i.e. categorical or ordinal. Such exposures could be recoded using binary variables to which one could apply the results of VanderWeele and Robins (2007, 2008). However, the theory concerning sufficient causes with polytomous variables is more subtle than that for binary variables. In particular, what VanderWeele & Robins (2008) formally defined as a sufficient cause interaction with binary exposures then has two analogues, weak and strong sufficient cause interactions. The two concepts have different implications for the interpretation of interactions.

Only in cases in which the exposures are binary will the two concepts coincide. As genetic exposures are often polytomous, it is the conditions that are derived in this paper which will most likely be of use in such applications.

2. NOTATION

We consider cases with two exposures in which one is binary and the other is ternary and also cases in which both are ternary. For the ternary exposures, we will consider cases in which these exposures are nominal categorical, i.e. the levels are unordered, and cases with ordered categories. The binary variables X and ternary variables V take values in $\{0, 1\}$ and $\{0, 1, 2\}$, respectively. We let D denote a dichotomous outcome; we index the population, assumed finite, by $\omega \in \Omega$. In cases in which one exposure is binary and the other ternary, we let $D_{xv}(\omega)$ denote the counterfactual value of D for individual ω if X and V were set, possibly contrary to fact, to values x and v , respectively. In cases in which both exposures are ternary, $D_{v_1v_2}(\omega)$ is defined analogously. To denote the indicator function that some random variable Z takes a value in the set S , we will use $I(Z \in S)$, or $I(Z = s)$ if S is a singleton. We let $\vee$ denote the disjunctive or OR operator defined for binary variables by $A \vee B = 0$ if $A = B = 0$ and $A \vee B = 1$ otherwise. For a binary variable A , we define $\bar{A} = 1 - A$. We will use $A \perp\!\!\!\perp B \mid C$ to denote that A is independent of B conditional on C . We will say that the effects of two exposures X and V , or V_1 and V_2 , on D are unconfounded given the covariates C if $D_{xv} \perp\!\!\!\perp (X, V) \mid C$ or $D_{v_1v_2} \perp\!\!\!\perp (V_1, V_2) \mid C$. If the two exposures are randomized, the effects of the two exposures on D will be unconfounded given $C = \emptyset$.

DEFINITION 1 (*Monotonic effect*). *For two ordinal variables V_1 and V_2 , we say that V_1 has a positive monotonic effect on D if, for all ω , $D_{v_1v_2}(\omega)$ is nondecreasing in v_1 for all v_2 ; monotonicity for v_2 is defined analogously.*

Negative monotonic effects could be defined analogously. Monotonicity will sometimes allow for stronger conclusions or for tests of weaker conditions.

3. SUFFICIENT CAUSE INTERACTIONS AND WEAK AND DEFINITE INTERDEPENDENCE

We begin our discussion with a definition of definite interdependence. Consider a binary variable X and a ternary variable V . Suppose there is an individual ω for whom $D_{xv}(\omega)$ would take the value 1 if $x = 1$ and $v = 2$ but for whom $D_{xv}(\omega) = 0$ if only one of these two conditions holds. In this case neither $x = 1$ nor $v = 2$ alone would be sufficient for the outcome but both conditions together would suffice. We will call examples like this cases of definite interdependence. More generally, we have the following definition.

DEFINITION 2 (*Definite interdependence*). *For any two variables V_1 and V_2 with support $\mathcal{T}_1$ and $\mathcal{T}_2$, respectively, we will say that there is definite interdependence between $I(V_1 \in S_1)$ and $I(V_2 \in S_2)$, where S_1 and S_2 are proper subsets of $\mathcal{T}_1$ and $\mathcal{T}_2$, if for some ω , $D_{v_1v_2}(\omega) = 1$ for $v_1 \in S_1, v_2 \in S_2$ but $D_{v_1v_2}(\omega) = 0$ for $v_1 \notin S_1, v_2 \in S_2$ and $D_{v_1v_2}(\omega) = 0$ for $v_1 \in S_1, v_2 \notin S_2$.*

We now also introduce a related notion, that of weak interdependence.

DEFINITION 3 (*Weak interdependence*). *For any two variables V_1 and V_2 , we will say there is weak interdependence between $I(V_1 = v_1)$ and $I(V_2 = v_2)$ if for some ω , $D_{v_1v_2}(\omega) = 1$ but $D_{v'_1v_2}(\omega) = 0$ for some $v'_1 \neq v_1$ and $D_{v_1v'_2}(\omega) = 0$ for some $v'_2 \neq v_2$.*

Definite interdependence between $I(V_1 = v_1)$ and $I(V_2 = v_2)$ thus implies that any change of one of the two variables from the levels $V_1 = v_1$ and $V_2 = v_2$, would change the outcome

from 1 to 0, whereas weak interdependence implies that for each of the two variables, there is some change from the levels $V_1 = v_1$ and $V_2 = v_2$ that would change the outcome from 1 to 0. Definite interdependence implies weak interdependence. Definition 2 extends the definition of definite interdependence given in VanderWeele & Robins (2007) for two binary variables to cases in which one or both variables are polytomous. If both variables were binary, the definitions of definite and weak interdependence would coincide. The definitions of definite and weak interdependence also apply to polytomous variables with more than three levels, but here we restrict our analysis to the simpler case of variables with up to three levels.

In what follows we will relate this definition of definite interdependence to the sufficient cause framework in which causation is conceived as a collection of causal mechanisms, each sufficient to bring about the outcome. We extend similar relations for binary variables (VanderWeele & Robins, 2008) to settings with polytomous exposures with three levels. Suppose then that X and V denoted environmental and genetic exposures respectively with V indicating 0, 1 or 2 variant alleles at a particular locus. The outcome D might denote a particular disease for which the exposures X and V are thought to be causes. Each mechanism or sufficient cause for D may or may not require a particular value of X or a particular value for V ; each mechanism might also require some other factors which, for the i th sufficient cause, we might denote by A_i . These variables constituting other factors are considered binary but may represent complex conjunctions and disjunctions of many other factors. We formalize these ideas below in the definition of a sufficient cause representation for D . Define $I(X = *) \equiv 1$ and $I(V = *) \equiv 1$.

DEFINITION 4 (Sufficient cause representation). For binary exposure X , ternary exposure V and binary outcome D , we say that $\vee_{i \in \{0,1,*\}, j \in \{0,1,2,*\}} A_{ij} I(x = i) I(v = j)$ constitutes a sufficient cause representation for D if the binary variables $A_{ij}(\omega)$ are functions of the counterfactual outcomes $\{D_{xv}(\omega)\}_{x \in \{0,1\}, v \in \{0,1,2\}}$ such that

$$D_{xv} = \vee_{i \in \{0,1,*\}, j \in \{0,1,2,*\}} A_{ij} I(x = i) I(v = j). \quad (1)$$

An analogous definition can be given for two ternary exposures. A sufficient cause representation expresses the counterfactual outcomes D_{xv} as a disjunction of terms, each of which involves the conjunction of some variable A_{ij} and possibly $I(x = i)$ and $I(v = j)$. Representation (1) written out in full gives

$$\begin{aligned} D_{xv} = & A_{**} \vee A_{0*} I(x = 0) \vee A_{1*} I(x = 1) \vee A_{*0} I(v = 0) \vee A_{*1} I(v = 1) \vee A_{*2} I(v = 2) \\ & \vee A_{00} I(x = 0) I(v = 0) \vee A_{01} I(x = 0) I(v = 1) \vee A_{02} I(x = 0) I(v = 2) \\ & \vee A_{10} I(x = 1) I(v = 0) \vee A_{11} I(x = 1) I(v = 1) \vee A_{12} I(x = 1) I(v = 2). \end{aligned} \quad (2)$$

There will always be at least one such representation for the counterfactual outcomes since we can define $A_{**} = A_{0*} = A_{1*} = A_{*0} = A_{*1} = A_{*2} = 0$ for all ω and $A_{ij}(\omega) = D_{ij}(\omega)$ for $i = 0, 1$, $j = 0, 1, 2$. Each conjunction in the disjunction in (2) could be referred to as a sufficient cause. In particular cases, only a subset of the 12 sufficient causes given in (2) may be present. For example, suppose there are only three causal mechanisms for the outcome D : one mechanism requiring the environmental exposure, $X = 1$, a single variant allele, $V = 1$, and some other unknown factors A_{11} ; one mechanism requiring two variant alleles, $V = 2$; and one mechanism requiring a particular value neither for the environmental nor for the genetic exposure but only the presence of some other factors A_{**} . If these were the only sufficient causes for D , we could write $D = A_{**} \vee I(V = 2) \vee A_{11} I(X = 1) I(V = 1)$.

In general there will be more than one sufficient cause representation. For example, if we had variables $A_{**}, A_{0*}, \dots, A_{12}$ for which (1) was satisfied and redefined $B_{0*} = \bar{A}_{**} A_{0*}$,

$B_{1*} = \bar{A}_{**}A_{1*}$, then $A_{**}, B_{0*}, B_{1*}, A_{*0}, \dots, A_{12}$ would also satisfy (1). For a particular choice of the variables $A_{**}, A_{0*}, \dots, A_{12}$ that satisfy (1), the various conjunctions in (1) may correspond to causal mechanisms for the outcome such that it is possible to conceive of interventions on these mechanisms. In such cases, the variables A_{ij} may also allow for a physical interpretation as complex conjunctions and disjunctions of other background factors. If it is not possible to conceive of interventions on the conjunctions in (1), it may be preferable to refer to the conjunctions in (1) as sufficient conjunctions for D rather than sufficient causes for D . However, as will be seen below, the results in this paper give conclusions concerning all possible sufficient cause representations for the outcome D . Thus provided there is some representation that corresponds to the mechanisms for D , the results below will be applicable. This brings us to two further definitions.

DEFINITION 5 (Weak sufficient cause interaction). *For binary exposure X and ternary exposure V , we will say that a weak sufficient cause interaction is present between $I(X = x)$ and $I(V = v)$ if in every sufficient cause representation for D there exists ω such that $A_{xv}(\omega) = 1$.*

DEFINITION 6 (Strong sufficient cause interaction). *We will say that a strong sufficient cause interaction is present between $I(X = x)$ and $I(V \in S)$, where S is a proper subset of $\{0, 1, 2\}$ if in every sufficient cause representation for D , there is some ω such that: $A_{xv}(\omega) = 1$ whenever $v \in S$; $A_{**}(\omega) = 0$; $A_{x'v}(\omega) = 0$ for $x' \in \{0, 1, *\} \setminus \{x\}$, $v \in S$; and $A_{xv'}(\omega) = 0$ for $v' \in \{0, 1, 2, *\} \setminus S$.*

Analogous definitions hold for two ternary exposures. If both exposures were binary then the definitions of weak and strong sufficient cause interactions would coincide, see details in the proof of Theorem 3 in VanderWeele & Robins (2008); thus, in the context of binary exposures, VanderWeele & Robins (2008) simply refer to sufficient cause interactions. We have the following relation, whose proof is in the Appendix. An analogous result holds for two ternary exposures. See the Supplementary Material.

THEOREM 1. *For binary exposure X and ternary exposure V , there is weak interdependence between $I(X = x)$ and $I(V = v)$ if and only if there is a weak sufficient cause interaction between $I(X = x)$ and $I(V = v)$; furthermore, there is definite interdependence between $I(X = x)$ and $I(V \in S)$ if and only if there is a strong sufficient cause interaction between $I(X = x)$ and $I(V \in S)$.*

4. TESTS FOR ONE BINARY EXPOSURE AND ONE TERNARY EXPOSURE

We develop empirical tests for weak and definite interdependence, or equivalently weak and strong sufficient cause interactions, and begin with the setting of binary exposure X and ternary exposure V . Let $p_{xvc} = \text{pr}(D = 1 \mid X = x, V = v, C = c)$.

PROPOSITION 1. *Suppose that V is ordinal, that X and V have positive monotonic effects on D , and that $D_{xv} \perp\!\!\!\perp (X, V) \mid C$. If for some value c and some $i \in \{1, 2\}$,*

$$p_{1ic} - p_{10c} - p_{0ic} + p_{00c} > 0,$$

then there is weak interdependence between $I(X = 1)$ and $I(V = i)$; if for some value c ,

$$p_{11c} - p_{10c} - p_{02c} + p_{00c} > 0,$$

then there is definite interdependence between $I(X = 1)$ and $I(V \in \{1, 2\})$; if for some value c ,

$$p_{12c} - p_{11c} - p_{02c} + p_{01c} > 0,$$

then there is definite interdependence between $I(X = 1)$ and $I(V = 2)$.

Provided that the effects of X and V on D are unconfounded given C , Proposition 1 gives empirical conditions for testing for weak or definite interdependence. However, Proposition 1 requires that both X and V have positive monotonic effects on D . In the next two propositions we will give other empirical conditions for testing for weak or definite interdependence which relax the assumption of monotonicity for X or for both X and V .

PROPOSITION 2. *Suppose that V is ordinal, that V has a positive monotonic effect on D and that $D_{XV} \perp\!\!\!\perp (X, V) \mid C$. If for some value c and some $i \in \{1, 2\}$,*

$$p_{1ic} - p_{10c} - p_{0ic} > 0,$$

then there is weak interdependence between $I(X = 1)$ and $I(V = i)$; if for some value c ,

$$p_{11c} - p_{10c} - p_{02c} > 0,$$

then there is definite interdependence between $I(X = 1)$ and $I(V \in \{1, 2\})$; if for some value c ,

$$p_{12c} - p_{11c} - p_{02c} > 0,$$

then there is definite interdependence between $I(X = 1)$ and $I(V = 2)$.

Proposition 2 makes no assumptions about the ordering of levels of X or about monotonicity of the effect of X , so one could test for weak or definite interdependence between $I(X = 0)$ and $I(V = 1)$, $I(V = 2)$ or $I(V \in \{1, 2\})$ by reversing the labelling 0 and 1 for X . For example, the first condition in Proposition 2 would become $p_{0ic} - p_{00c} - p_{1ic} > 0$ to test for weak interdependence between $I(X = 0)$ and $I(V = i)$ rather than $p_{1ic} - p_{10c} - p_{0ic} > 0$ to test for weak interdependence between $I(X = 1)$ and $I(V = i)$. Similarly, in Proposition 3 below there will be no assumptions made about the ordering of levels of V . If other levels of V are of interest, analogous conditions can be derived by relabelling levels.

PROPOSITION 3. *Suppose that $D_{XV} \perp\!\!\!\perp (X, V) \mid C$. If for some value c ,*

$$p_{12c} - p_{1ic} - p_{02c} > 0$$

for $i = 0$ or $i = 1$, then there is weak interdependence between $I(X = 1)$ and $I(V = 2)$; if for some value c ,

$$p_{12c} - p_{10c} - p_{11c} - p_{02c} > 0,$$

then there is definite interdependence between $I(X = 1)$ and $I(V = 2)$.

The proof of Proposition 3 indicates that if the first condition is satisfied for some i then there will be some individual ω such that $D_{12}(\omega) = 1$ and $D_{1i}(\omega) = D_{02}(\omega) = 0$. If only the binary exposure X has a monotonic effect on D , the conditions in Proposition 3 can be used to test for weak or definite interdependence. If the binary exposure X has a monotonic effect on D , and if the condition $p_{12c} - p_{10c} - p_{11c} - p_{02c} > 0$ is satisfied so that there is definite interdependence between $I(X = 1)$ and $I(V = 2)$, then not only is there an individual ω for whom $D_{12}(\omega) = 1$ and $D_{10}(\omega) = D_{11}(\omega) = D_{02}(\omega) = 0$ but by monotonicity it is moreover the case that for individual ω , $D_{01}(\omega) = D_{00}(\omega) = 0$.

The conditions in Propositions 1–3 are sufficient but not necessary for weak and definite interdependence. Also, definite interdependence may be present even if we can only detect weak interdependence. Such remarks hold also for Propositions 4–6 below.

5. TESTS FOR TWO TERNARY EXPOSURES

We now turn to the case of two ternary exposures V_1 and V_2 . Let $p_{v_1v_2c} = \text{pr}(D = 1 \mid V_1 = v_1, V_2 = v_2, C = c)$. For Propositions 4 and 6 the roles of V_1 and V_2 are symmetric.

PROPOSITION 4. *Suppose that V_1 and V_2 are ordinal, that V_1 and V_2 have positive monotonic effects on D , and that $D_{v_1v_2} \perp\!\!\!\perp (V_1, V_2) \mid C$. If for some value c ,*

$$p_{11c} - p_{10c} - p_{01c} + p_{00c} > 0,$$

then there is weak interdependence between $I(V_1 = 1)$ and $I(V_2 = 1)$; if for some value c ,

$$p_{12c} - p_{1ic} - p_{02c} + p_{0ic} > 0$$

for $i = 0$ or $i = 1$, then there is weak interdependence between $I(V_1 = 1)$ and $I(V_2 = 2)$; if for some $v_1 \neq 2$, and some $v_2 \neq 2$, and some c ,

$$p_{22c} - p_{2v_2c} - p_{v_12c} + p_{v_1v_2c} > 0,$$

then there is weak interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$; if for some value c ,

$$p_{11c} - p_{20c} - p_{02c} + p_{00c} > 0,$$

then there is definite interdependence between $I(V_1 \in \{1, 2\})$ and $I(V_2 \in \{1, 2\})$; if for some value c ,

$$p_{12c} - p_{02c} - p_{21c} + p_{01c} > 0,$$

then there is definite interdependence between $I(V_1 \in \{1, 2\})$ and $I(V_2 = 2)$; if for some value c ,

$$p_{22c} - p_{21c} - p_{12c} + p_{11c} > 0,$$

then there is definite interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$.

In some parts of Proposition 4, only one of two or more conditions is required. For example, if $p_{12c} - p_{1ic} - p_{02c} + p_{0ic} > 0$ for $i = 0$ or $i = 1$ then there will be weak interdependence between $I(V_1 = 1)$ and $I(V_2 = 2)$; if this holds for a particular i then for some individual ω such that $D_{12}(\omega) = 1$ and $D_{1i}(\omega) = D_{02}(\omega) = 0$. Similar remarks hold for Propositions 5 and 6 below.

Proposition 5 requires that only one of the two variables, say V_1 , is ordinal and has a monotonic effect on D . Proposition 5 takes $V_2 = 2$ as the level of interest and gives conditions for weak or definite interdependence between $I(V_2 = 2)$ and one of $I(V_1 = 1)$, $I(V_1 = 2)$ or $I(V_1 = \{1, 2\})$. If weak or definite interdependence between $I(V_2 = 0)$ or $I(V_2 = 1)$ and one of $I(V_1 = 1)$, $I(V_1 = 2)$ or $I(V_1 = \{1, 2\})$ is of interest then similar conditions can be obtained by relabelling the levels of V_2 .

PROPOSITION 5. *Suppose that V_1 is ordinal, that V_1 has a positive monotonic effect on D , and that $D_{v_1v_2} \perp\!\!\!\perp (V_1, V_2) \mid C$. If for some value c ,*

$$p_{12c} - p_{1ic} - p_{02c} > 0$$

for $i = 0$ or $i = 1$, then there is weak interdependence between $I(V_1 = 1)$ and $I(V_2 = 2)$; if for some value c ,

$$p_{22c} - p_{2ic} - p_{02c} > 0$$

for $i = 0$ or $i = 1$, then there is weak interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$; if for some value c ,

$$p_{12c} - p_{21c} - p_{20c} - p_{02c} > 0,$$

then there is definite interdependence between $I(V_1 = \{1, 2\})$ and $I(V_2 = 2)$; if for some value c ,

$$p_{22c} - p_{21c} - p_{20c} - p_{12c} > 0,$$

then there is definite interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$.

Proposition 6 provides empirical conditions for weak and definite interdependence without requiring either V_1 or V_2 to have monotonic effects on D . We give conditions for weak or definite interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$. As with Proposition 5, if other levels of V_1 or V_2 are of interest, similar conditions can be obtained simply by relabelling the levels of V_1 and V_2 .

PROPOSITION 6. *Suppose that $D_{v_1v_2} \perp\!\!\!\perp (V_1, V_2) \mid C$. If for some $v_1 \neq 2$, and some $v_2 \neq 2$, and some value c ,*

$$p_{22c} - p_{2v_2c} - p_{v_12c} > 0,$$

then there is weak interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$; if for some value c ,

$$p_{22c} - p_{21c} - p_{20c} - p_{12c} - p_{02c} > 0,$$

then there is definite interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$.

6. CONDITIONS FOR SUFFICIENT CAUSE INTERACTIONS IN LINEAR AND LOG-LINEAR MODELS

We now relate the conditions for weak and definite interdependence, and thus for weak and strong sufficient cause interactions, to regression coefficients for interaction terms in linear and log-linear models. For simplicity we will initially assume that the effects of the two exposures on the outcome are unconfounded. For binary exposure X and ternary exposure V , let $X_1 = X$, $X_2 = I(V \in \{1, 2\})$ and $X_3 = I(V = 2)$. Then a saturated Bernoulli regression model with identity link is given by

$$\begin{aligned} \text{pr}(D = 1 \mid X = x, V = v) &= \text{pr}(D = 1 \mid X_1 = x_1, X_2 = x_2, X_3 = x_3) \\ &= \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 + \alpha_4 x_1 x_2 + \alpha_5 x_1 x_3. \end{aligned} \quad (3)$$

For two ternary variables V_1 and V_2 , let $X_1 = I(V_1 \in \{1, 2\})$, $X_2 = I(V_1 = 2)$, $X_3 = I(V_2 \in \{1, 2\})$ and $X_4 = I(V_2 = 2)$. Then a saturated Bernoulli regression model with identity link is given by

$$\begin{aligned} \text{pr}(D = 1 \mid V_1 = v_1, V_2 = v_2) \\ = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_3 + \alpha_4 x_4 + \alpha_5 x_1 x_3 + \alpha_6 x_1 x_4 + \alpha_7 x_2 x_3 + \alpha_8 x_2 x_4. \end{aligned} \quad (4)$$

There are six probabilities of the form p_{xv} and nine of the form $p_{v_1v_2}$; the models given in (3) and (4) have six and nine parameters, respectively, and are saturated. The conditions given in Propositions 1–3 and 4–6 can be expressed in terms of the regression parameters of models (3) and (4), and are summarized in Tables 1 and 2, respectively.

For a binary variable and a ternary variable, the analogous saturated log-linear model is given by

$$\log\{\text{pr}(D = 1 \mid X = x, V = v)\} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_1 x_2 + \beta_5 x_1 x_3. \quad (5)$$

For two ternary variables, the analogous saturated log-linear model is given by

$$\begin{aligned} \log\{\text{pr}(D = 1 \mid V_1 = v_1, V_2 = v_2)\} \\ = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_1 x_3 + \beta_6 x_1 x_4 + \beta_7 x_2 x_3 + \beta_8 x_2 x_4. \end{aligned} \quad (6)$$

Table 1. *Relationships between regression coefficients in a saturated Bernoulli regression model with linear link and conditions for weak or strong sufficient cause interactions for a binary exposure X and an exposure V with three levels*

Monotonicity assumptions	Form of interdependence	Condition on regression coefficients
X and V monotonic	Weak: $1(X = 1)$ and $1(V = 1)$	$\alpha_4 > 0$
	Weak: $1(X = 1)$ and $1(V = 2)$	$\alpha_4 + \alpha_5 > 0$
	Definite: $1(X = 1)$ and $1(V \in \{1, 2\})$	$\alpha_4 - \alpha_3 > 0$
	Definite: $1(X = 1)$ and $1(V = 2)$	$\alpha_5 > 0$
V monotonic	Weak: $1(X = 1)$ and $1(V = 1)$	$\alpha_4 - \alpha_0 > 0$
	Weak: $1(X = 1)$ and $1(V = 2)$	$\alpha_4 + \alpha_5 - \alpha_0 > 0$
	Definite: $1(X = 1)$ and $1(V \in \{1, 2\})$	$\alpha_4 - \alpha_3 - \alpha_0 > 0$
	Definite: $1(X = 1)$ and $1(V = 2)$	$\alpha_5 - \alpha_2 - \alpha_0 > 0$
No monotonicity assumption on V irrespective of whether X is monotonic	Weak: $1(X = 1)$ and $1(V = 2)$	$\alpha_4 + \alpha_5 - \alpha_0 > 0$ or $\alpha_5 - \alpha_2 - \alpha_0 > 0$
	Definite: $1(X = 1)$ and $1(V = 2)$	$\alpha_5 - \alpha_2 - \alpha_1 - 2\alpha_0 > 0$

Table 2. *Relationships between regression coefficients in a saturated Bernoulli regression model with linear link and conditions for weak or strong sufficient cause interactions for two categorical or ordinal exposures, V_1 and V_2 , each with three levels*

Monotonicity assumptions	Form of interdependence	Condition on regression coefficients
V_1 and V_2 monotonic	Weak: $1(V_1 = 1)$ and $1(V_2 = 1)$	$\alpha_5 > 0$
	Weak: $1(V_1 = 1)$ and $1(V_2 = 2)$	$\alpha_5 + \alpha_6 > 0$ or $\alpha_6 - \alpha_3 + \alpha_1 > 0$
	Weak: $1(V_1 = 2)$ and $1(V_2 = 1)$	$\alpha_5 + \alpha_7 > 0$ or $\alpha_7 - \alpha_1 + \alpha_3 > 0$
	Weak: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_5 + \alpha_6 + \alpha_7 + \alpha_8 > 0$ or $\alpha_6 + \alpha_8 > 0$ or $\alpha_7 + \alpha_8 > 0$ or $\alpha_8 > 0$
	Definite: $1(V_1 \in \{1, 2\})$ and $1(V_2 \in \{1, 2\})$	$\alpha_5 - \alpha_4 - \alpha_2 > 0$
	Definite: $1(V_1 \in \{1, 2\})$ and $1(V_2 = 2)$	$\alpha_6 - \alpha_7 - \alpha_2 > 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 \in \{1, 2\})$	$\alpha_7 - \alpha_6 - \alpha_4 > 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_8 > 0$
V_1 monotonic	Weak: $1(V_1 = 1)$ and $1(V_2 = 2)$	$\alpha_5 + \alpha_6 - \alpha_0 > 0$ or $\alpha_6 - \alpha_3 - \alpha_0 > 0$
	Weak: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_5 + \alpha_6 + \alpha_7 + \alpha_8 - \alpha_0 > 0$ or $\alpha_6 + \alpha_8 - \alpha_3 - \alpha_0 > 0$
	Definite: $1(V_1 \in \{1, 2\})$ and $1(V_2 = 1)$	$\alpha_6 - \alpha_7 - \alpha_3 - 2\alpha_2 - \alpha_1 - 2\alpha_0 > 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_8 - \alpha_5 - \alpha_3 - \alpha_2 - 2\alpha_1 - 2\alpha_0 > 0$
No monotonicity assumption on V_1 nor V_2	Weak: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_5 + \alpha_6 + \alpha_7 + \alpha_8 - \alpha_0 > 0$ or $\alpha_6 + \alpha_8 - \alpha_3 - \alpha_0 > 0$ or $\alpha_7 + \alpha_8 - \alpha_1 - \alpha_0 > 0$ or $\alpha_8 - \alpha_5 - \alpha_3 - \alpha_1 - \alpha_0 > 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\alpha_8 - \alpha_5 - \alpha_4 - 2\alpha_3 - \alpha_2 - 2\alpha_1 - 3\alpha_0 > 0$

It is shown in the Appendix that the conditions in Propositions 1–3 and 4–6 are satisfied if the conditions on the regression coefficients of log-linear models (5) and (6) given in Tables 3 and 4, respectively, are satisfied. In Tables 1 and 2, the conditions on the regression coefficients of a linear model are equivalent to the conditions given in Propositions 1–6, whereas the conditions on the coefficients of a log-linear model given in Tables 3 and 4 are only sufficient for the conditions in Propositions 1–6; they are not equivalent. The conditions in Tables 3 and 4 are still of interest because in certain genetic study designs, such as the case-only design (Yang et al., 1999), sometimes only the interaction parameters of a log-linear model can be estimated.

If the effect of X or V is monotonic on average, i.e. $E(D \mid X = x, V = v)$ is nondecreasing in x or v then, for model (3), we will have respectively that $\beta_1 \geq 0$ and $\beta_1 + \beta_4 \geq 0$ or that

Table 3. Relationships between regression coefficients in a saturated Bernoulli regression model with log-linear link and conditions for weak or strong sufficient cause interactions for a binary exposure X and an exposure V with three levels

Monotonicity assumptions	Form of interdependence	Condition on regression coefficients
X and V monotonic		As in Table 1, but with β_r replacing α_r
V monotonic	Weak: $1(X = 1)$ and $1(V = 1)$	$\beta_4 > \log(2)$ and $\beta_1 \geq 0$
	Weak: $1(X = 1)$ and $1(V = 2)$	$\beta_4 + \beta_5 > \log(2)$ and $\beta_1 \geq 0$
	Definite: $1(X = 1)$ and $1(V \in \{1, 2\})$	$\beta_4 - \beta_3 > \log(2)$ and $\beta_1 \geq 0$
	Definite: $1(X = 1)$ and $1(V = 2)$	$\beta_5 > \log(2)$ and $\beta_1 + \beta_4 \geq 0$
No monotonicity assumption on V irrespective of whether X is monotonic	Weak: $1(X = 1)$ and $1(V = 2)$	$\beta_5 > \log(2)$ and $\beta_1 + \beta_4 \geq 0$ and either $\beta_3 \geq 0$ or $\beta_2 + \beta_3 + \beta_4 \geq 0$
	Definite: $1(X = 1)$ and $1(V = 2)$	$\beta_5 > \log(3)$ and $\beta_1 + \beta_4 \geq 0$, $\beta_3 \geq 0$, $\beta_2 + \beta_3 + \beta_4 \geq 0$

Table 4. Relationships between regression coefficients in a saturated Bernoulli regression model with linear link and conditions for weak or strong sufficient cause interactions for two categorical or ordinal exposures, V_1 and V_2 , each with three levels

Monotonicity assumptions	Form of interdependence	Condition on regression coefficients
V_1 and V_2 monotonic		As in Table 2, but with β_r replacing α_r
V_1 monotonic	Weak: $1(V_1 = 1)$ and $1(V_2 = 2)$	$\beta_5 + \beta_6 > \log(2)$ and $\beta_3 + \beta_4 \geq 0$ or $\beta_6 > \log(2)$ and $\beta_4 \geq 0$
	Weak: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\beta_5 + \beta_6 + \beta_7 + \beta_8 > \log(2)$ and $\beta_3 + \beta_4 \geq 0$ or $\beta_6 + \beta_8 > \log(2)$ and $\beta_4 \geq 0$
	Definite: $1(V_1 \in \{1, 2\})$ and $1(V_2 = 1)$	$\beta_6 - \beta_7 - \beta_2 > \log(3)$ and $\beta_4 \geq 0$, $\beta_3 + \beta_4 + \beta_5 + \beta_7 \geq 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\beta_8 > \log(3)$ and $\beta_4 + \beta_6 \geq 0$, $\beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 \geq 0$
No monotonicity assumptions on V_1 nor V_2	Weak: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\beta_5 + \beta_6 + \beta_7 + \beta_8 > \log(2)$ and $\beta_1 + \beta_2 \geq 0$, $\beta_3 + \beta_4 \geq 0$ or $\beta_6 + \beta_8 > \log(2)$ and $\beta_4 \geq 0$, $\beta_1 + \beta_2 + \beta_5 + \beta_7 \geq 0$ or $\beta_7 + \beta_8 > \log(2)$ and $\beta_2 \geq 0$, $\beta_3 + \beta_4 + \beta_5 + \beta_6 \geq 0$ or $\beta_8 > \log(2)$ and $\beta_2 + \beta_7 \geq 0$, $\beta_4 + \beta_6 \geq 0$
	Definite: $1(V_1 = 2)$ and $1(V_2 = 2)$	$\beta_8 > \log(4)$ and $\beta_2 + \beta_7 \geq 0$, $\beta_4 + \beta_6 \geq 0$, $\beta_1 + \beta_2 + \beta_5 + \beta_6 + \beta_7 \geq 0$, $\beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 \geq 0$

$\beta_2 \geq 0$, $\beta_2 + \beta_4 \geq 0$ and $\beta_3 \geq 0$, even if the individual-level assumption of monotonic effects does not hold. Consequently, if the effects of X and V on D are monotonic on average then all of the non-strict inequalities in Table 3 will hold and only the strict inequalities would need to be tested. Likewise, in model (4) if the effects of V_1 and V_2 are monotonic on average in that $E(D | V_1 = v_1, V_2 = v_2)$ is nondecreasing in v_1 and v_2 , then all of the non-strict inequalities in Table 4 will hold. For example, to test for definite interdependence between $I(V_1 = 2)$ and $I(V_2 = 2)$, one need only test $\beta_8 > 0$ if one is willing to assume that the effects of V_1 and V_2 are monotonic, or $\beta_8 > \log(3)$ if it is only assumed that the effect of V_1 is monotonic or $\beta_8 > \log(4)$ if no monotonicity assumptions are made on the effects of V_1 and V_2 .

An alternative parameterization of model (1) or (3) might use $X_2 = I(V = 1)$ and $X_3 = I(V = 2)$, rather than $X_2 = I(V \in \{1, 2\})$ and $X_3 = I(V = 2)$; similarly, in model (2) or (4), we might instead let $X_1 = I(V_1 = 1)$, $X_2 = I(V_1 = 2)$, $X_3 = I(V_2 = 1)$, $X_4 = I(V_2 = 2)$. If we let α_i^* and β_i^* denote the regression coefficients for models (3) or (4) and (5) or (6), respectively, then, under such alternative parameterizations, the conditions in Tables 1–4 can easily be re-expressed in terms of α_i^* and β_i^* rather than α_i and β_i . For example, we can use $\alpha_3 = \alpha_3^* - \alpha_2^*$, $\alpha_5 = \alpha_5^* - \alpha_4^*$, $\alpha_i = \alpha_i^*$ for $i = 0, 1, 2, 4$ for Table 1 and $\alpha_2 = \alpha_2^* - \alpha_1^*$, $\alpha_4 = \alpha_4^* - \alpha_3^*$, $\alpha_6 = \alpha_6^* - \alpha_5^*$,

$\alpha_7 = \alpha_7^* - \alpha_5^*$, $\alpha_8 = \alpha_8^* - \alpha_7^* - \alpha_6^* + \alpha_5^*$, $\alpha_i = \alpha_i^*$ for $i = 0, 1, 3, 5$ for Table 3. Analogous relations hold between β_i and β_i^* in Tables 2 and 4.

Suppose there is some set of variables C such that the effects of X and V or of V_1 and V_2 on D are unconfounded given C . In cases in which C contains many variables or continuous variables, one might incorporate the confounding variables into one of models (5) or (6); for example, with model (5) one might have

$$\log\{\text{pr}(D = 1 \mid x, v, c)\} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_1 x_2 + \beta_5 x_1 x_3 + g(c, \gamma) \quad (7)$$

for some parameter vector γ . It is easily verified that under model (7), for example, the conditions given in Table 3 will again imply the conditions in Propositions 1–3, provided that the model is correctly specified. The log-linear model (7) has the property that each condition in Propositions 1–3 either holds for all values of c or does not hold for any value of c . Analogous remarks hold for Table 4, Propositions 4–6 and the incorporation of confounding variables into log-linear model (6). In contrast, if the term $g(c, \gamma)$ were added to linear models (3) and (4) rather than to log-linear models (5) and (6), then this property would only hold for the conditions in Propositions 1 and 4; it would not hold for the conditions in Propositions 2, 3, 5 and 6.

The conditions of Propositions 1–6 could also be expressed in terms of the parameters of a logistic model; however, the expressions would be considerably more complicated than those in Tables 1–6; moreover, for none of the conditions in Propositions 1–6 is it the case that either the condition holds for all values of c or it does not hold for any; the conditions would have to be tested separately for each c . However, if the outcome is rare in all strata of the exposures and confounding variables, then regression coefficients for log links will approximate those for logistic links because the denominator of the odds ratio, $\text{pr}(D \mid \cdot) / \{1 - \text{pr}(D \mid \cdot)\}$, would be approximately unity. Thus, in a setting in which the rare outcome assumption is reasonable, the results in Tables 3 and 4 could still be used for logistic regression models and in such settings these tests would be applicable even with case-control data. We make use of this observation in the applications below.

When using these log-linear or logistic models, the conclusion of weak or definite interdependence will clearly depend on correct model specification. This may be problematic because the specification of a model such as (7) will impose restrictions on the relationship between the confounding variables C and the background causes A_{ij} in the sufficient cause model (VanderWeele et al., 2010). An alternative approach that partially circumvents this difficulty is to use marginal structural models (Robins et al., 2000) or doubly robust tests (Vansteelandt et al., 2008) to test marginalized versions of the conditions in Propositions 1–6 (VanderWeele et al., 2010).

7. APPLICATIONS

In this section we will consider the implications of the results above for two recent studies concerning gene-gene and gene-environment interactions. For each we examine the extent to which the odds ratio estimates obtained in the study could be used as evidence for sufficient cause interactions. These examples are used for illustrative purposes. A more thorough examination would require re-analysis of the data using one of the approaches described in the previous section to specifically test for sufficient cause gene-gene and gene-environment interactions.

van Rooij et al. (2003) consider gene-environment interaction between the periconceptual use of a folic acid supplement and MTHFR* C677 genotype variants on the risk of giving birth to an infant with cleft lip, with or without cleft palate. The mother's MTHFR* C677 genotype can be categorized as CC, CT or TT; folic acid supplement use is a dichotomous exposure. The C677 CC genotype, with use of a folic acid supplement, was taken as the reference group.

We will let $V = 0$, $V = 1$ and $V = 2$ denote respectively the CC, CT and TT genotypes, and we will let $X = 0$ denote use of folic acid supplements and $X = 1$ denote no supplement use. In a case-control study, the authors obtained an adjusted odds ratio of 5.9 comparing mothers with the C677 TT genotype with no folic acid supplement, $X = 1$, $V = 2$, to the reference category of C677 CC genotype with use of a folic acid supplement, $X = 0$, $V = 0$; the confidence interval for this estimate was (1.1, 30.9). None of the other comparisons with the reference group were statistically significant. If we are willing to assume that all of these other odds ratios are 1 and we are willing to make the rare disease assumption, then we could conclude that the estimate of β_5 in model (5) is $\log(5.9) = 1.77$ with a confidence interval of (0.10, 3.43). The results presented in Table 3 imply that a strong sufficient cause interaction, i.e. definite interdependence, is present if $\beta_5 > \log(3)$ without making monotonicity assumptions, or if $\beta_5 > \log(2)$ and it can be assumed that the effect of V on the outcome is monotonic, or if $\beta_5 > 0$ and it can be assumed that the effects of X and V on the outcome are monotonic. The conditions $\beta_5 > \log(3)$, $\beta_5 > \log(2)$ and $\beta_5 > 0$ are all satisfied by the point estimate, $\log(5.9)$. However, only for the final condition $\beta_5 > 0$, which applies when it can be assumed that the effects of both X and V on the outcome are monotonic, does the condition apply to the entire confidence interval (0.10, 3.43). In this case, if it can be assumed that the effects of both X and V on the outcome are monotonic, subject to the caveats of no unmeasured confounding and correct model specification, the odds ratio estimate could be interpreted as evidence that there was a mechanism that required both the C677 TT genotype and the absence of a folic acid supplement to operate, i.e. as evidence of a strong sufficient cause interaction.

Zhang et al. (2005) report the results of a case-control study concerning the lung cancer risk associated with ADPRT Val762Ala and XRCC1 Arg399Gln polymorphisms. Let the ADPRT Val/Val, Val/Ala and Ala/Ala genotypes be denoted by $V_1 = 0$, $V_1 = 1$ and $V_1 = 2$, respectively. Let the XRCC1 Arg/Arg, Arg/Gln, Gln/Gln genotypes be denoted by $V_2 = 0$, $V_2 = 1$ and $V_2 = 2$, respectively. In the notation of § 6 and under the rare disease assumption, the authors test for $\beta_8^* > 0$, equivalently, in the parameterization given in model (6), $\beta_8 + \beta_7 + \beta_6 + \beta_5 > 0$, using logistic regression adjusting for sex, age and smoking status. They obtain a p -value for this test of 0.018. Under the assumptions of no unmeasured confounding and correct model specification, it follows from Table 4 that one could conclude the presence of a weak sufficient cause interaction between $I(V_1 = 2)$ and $I(V_2 = 2)$ provided that the effects of V_1 and V_2 on the outcome were monotonic. Specifically, one could then conclude that there were individuals for whom a particular mechanism for the outcome would operate if $V_1 = 2$ and $V_2 = 2$ but would not operate if either $V_1 = 0$ or $V_2 = 0$. Further conclusions about sufficient cause interactions cannot be determined by the results reported by Zhang et al. (2005) and would require re-analysis of the data.

8. DISCUSSION

Our results cover many genetic association studies examining gene-gene or gene-environment interaction, but have limitations. First, they require adequate control for exposure-outcome confounders. Second, if modelling is used for confounding control, the conclusions will depend on correct model specification. Third, the conditions given in this paper are sufficient but not necessary for the presence of a sufficient cause interaction; a weak or strong sufficient cause interaction may be present but not identified. Fourth, our conditions for sufficient cause interactions are generally stronger than the presence of a statistical interaction and thus may require a larger sample size or effect size to detect. This final limitation is not surprising, as the conditions for sufficient cause interactions allow for conclusions about mechanisms that are considerably stronger than the mere presence of a statistical interaction.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *Biometrika* online.

APPENDIX

Proof of Theorem 1. We will show this holds for $X = 1$ and $V = 2$; the proof for any other values of X and V is similar. Suppose $I(X = 1)$ and $I(V = 2)$ exhibit weak interdependence, then for some ω , $D_{12}(\omega) = 1$ but $D_{02}(\omega) = 0$ and $D_{1v'}(\omega) = 0$ for some $v' \neq 2$; without loss of generality, assume $D_{1v'}(\omega) = 0$ for $v' = 1$. For any sufficient cause representation, we then have $0 = D_{02}(\omega) = A_{**}(\omega) \vee A_{0*}(\omega) \vee A_{*2}(\omega) \vee A_{02}(\omega)$ and thus that $A_{**}(\omega) = A_{*2}(\omega) = 0$; we also have that $0 = D_{11}(\omega) = A_{**}(\omega) \vee A_{1*}(\omega) \vee A_{*1}(\omega) \vee A_{11}(\omega)$ and thus $A_{1*}(\omega) = 0$; therefore we also have that $1 = D_{12}(\omega) = A_{**}(\omega) \vee A_{1*}(\omega) \vee A_{*2}(\omega) \vee A_{12}(\omega) = A_{12}(\omega)$. Since $A_{12}(\omega) = 1$ for any sufficient cause representation, there is a weak sufficient cause interaction between $I(X = 1)$ and $I(V = 2)$. We now prove the converse. Suppose that there is a weak sufficient cause interaction between $I(X = 1)$ and $I(V = 2)$ and suppose that $I(X = 1)$ and $I(V = 2)$ do not exhibit weak interdependence. Let $A_{**}, A_{0*}, \dots, A_{12}$ denote variables for any sufficient cause representation. In this representation, for each ω such that $A_{12}(\omega) = 1$ we have that $D_{12}(\omega) = 1$ and if $I(X = 1)$ and $I(V = 2)$ do not exhibit weak interdependence then we would have that one of $D_{02}(\omega) = 1$ or $D_{11}(\omega) = 1$ or $D_{10}(\omega) = 1$. For ω such that $D_{12}(\omega) = 1$, we could then define, $B_{12}(\omega) = 0$; $B_{02}(\omega) = 1$ if $D_{02}(\omega) = 1$ and $B_{02}(\omega) = 0$ otherwise; $B_{11}(\omega) = 1$ if $D_{11}(\omega) = 1$ and $B_{11}(\omega) = 0$ otherwise; and $B_{10}(\omega) = 1$ if $D_{10}(\omega) = 1$ and $B_{10}(\omega) = 0$ otherwise. For ω such that $D_{12}(\omega) \neq 1$, we could define, $B_{12}(\omega) = A_{12}(\omega)$, $B_{02}(\omega) = A_{02}(\omega)$, $B_{11}(\omega) = A_{11}(\omega)$, $B_{10}(\omega) = A_{10}(\omega)$. Then we would have that $B_{12}(\omega) = 0$ for all ω and

$$\begin{aligned} & A_{**} \vee A_{0*}I(x = 0) \vee A_{1*}I(x = 1) \vee A_{*0}I(v = 0) \vee A_{*1}I(v = 1) \vee A_{*2}I(v = 2) \\ & \vee A_{00}I(x = 0)I(v = 0) \vee A_{01}I(x = 0)I(v = 1) \vee B_{02}I(x = 0)I(v = 2) \\ & \vee B_{10}I(x = 1)I(v = 0) \vee B_{11}I(x = 1)I(v = 1) \end{aligned}$$

would be a sufficient cause representation for D . We would thus have a sufficient cause representation for D such that $B_{12}(\omega) = 0$ for all ω . We have thus shown that if there is a weak sufficient cause interaction between $I(X = 1)$ and $I(V = 2)$ then $I(X = 1)$ and $I(V = 2)$ must exhibit weak interdependence.

Now suppose that $I(X = x)$ and $I(V \in S)$ exhibit definite interdependence where S is a proper subset of $\{0, 1, 2\}$, then for some ω , $D_{xv}(\omega) = 1$ whenever $v \in S$ but $D_{x'v}(\omega) = 0$ for $x' \neq x$, $v \in S$ and $D_{xv'}(\omega) = 0$ for $v' \notin S$. For any sufficient cause representation it then follows that $A_{**}(\omega) = A_{x*}(\omega) = 0$; $A_{*v}(\omega) = 0$ for $v \in S$; $A_{x'v}(\omega) = 0$ for $x' \neq x$, $v \in S$; and $A_{xv'}(\omega) = 0$ for $v' \notin S$. From this it also follows that for $v \in S$, $1 = D_{xv}(\omega) = A_{**}(\omega) \vee A_{x*}(\omega) \vee A_{*v}(\omega) \vee A_{xv}(\omega) = A_{xv}(\omega)$ and thus there is a strong sufficient cause interaction between $I(X = x)$ and $I(V \in S)$. Conversely, suppose that there is a strong sufficient cause interaction between $I(X = x)$ and $I(V \in S)$ then in every sufficient cause representation for D , there is some ω such that: $A_{xv}(\omega) = 1$ for $v \in S$; $A_{**}(\omega) = 0$; $A_{x'v}(\omega) = 0$ for $x' \in \{0, 1, *\} \setminus \{x\}$, $v \in S$; and $A_{xv'}(\omega) = 0$ for $v' \in \{0, 1, 2, *\} \setminus S$. For this ω , for $v \in S$, $D_{xv}(\omega) = 1$ because $A_{xv}(\omega) = 1$; and for $x' \neq x$, $v \in S$, $D_{x'v}(\omega) = A_{**}(\omega) \vee A_{x'*}(\omega) \vee A_{*v}(\omega) \vee A_{x'v}(\omega) = 0$; and for $v' \notin S$, $D_{xv'}(\omega) = A_{**}(\omega) \vee A_{x*}(\omega) \vee A_{*v'}(\omega) \vee A_{xv'}(\omega) = 0$. Thus $I(X = x)$ and $I(V \in S)$ exhibit definite interdependence. $\square$

Proof of Proposition 1. If there is no individual ω for whom $D_{1i}(\omega) = 1$ and $D_{10}(\omega) = D_{0i}(\omega) = 0$, then by monotonicity, for all ω , $D_{1i}(\omega) - D_{10}(\omega) - D_{0i}(\omega) + D_{00}(\omega) \leq 0$ and taking expectations conditional on $C = c$, we obtain $p_{1ic} - p_{10c} - p_{0ic} + p_{00c} = E(D_{1i} | X = 1, V = i, C = c) - E(D_{10} | X = 1,$

$V = 0, C = c) - E(D_{0i} | X = 0, V = i, C = c) + E(D_{00} | X = 0, V = 0, C = c) = E(D_{1i} - D_{10} - D_{0i} + D_{00} | C = c) \leq 0$, where the final equality follows because $D_{XV} \perp\!\!\!\perp (X, V) | C$. Thus if $p_{1ic} - p_{10c} - p_{0ic} + p_{00c} > 0$, there is weak interdependence between $I(X = 1)$ and $I(V = i)$. Similarly, if there is no individual ω for whom $D_{11}(\omega) = 1$ and $D_{10}(\omega) = D_{02}(\omega) = 0$, then by monotonicity, for all ω , $D_{11}(\omega) - D_{10}(\omega) - D_{02}(\omega) + D_{00}(\omega) \leq 0$ and taking expectations conditional on $C = c$, we obtain $p_{11c} - p_{10c} - p_{02c} + p_{00c} \leq 0$. Thus if $p_{11c} - p_{10c} - p_{02c} + p_{00c} > 0$ then there exists ω such that $D_{11}(\omega) = 1$ and $D_{10}(\omega) = D_{02}(\omega) = 0$ and by monotonicity also $D_{12}(\omega) = 1$ and $D_{01}(\omega) = D_{00}(\omega) = 0$ and thus there is definite interdependence between $I(X = 1)$ and $I(V \in \{1, 2\})$. The proof of the third part of the proposition is similar. $\square$

Proof of Proposition 2. If $p_{1ic} - p_{10c} - p_{0ic} > 0$ then there is an ω for which $D_{1i}(\omega) = 1$ and $D_{10}(\omega) = D_{0i}(\omega) = 0$ and thus weak interdependence between $I(X = 1)$ and $I(V = i)$. Similarly, if $p_{11c} - p_{10c} - p_{02c} > 0$ then there is an ω for which $D_{11}(\omega) = 1$ and $D_{10}(\omega) = D_{02}(\omega) = 0$ and by monotonicity also $D_{12}(\omega) = 1$ and $D_{01}(\omega) = D_{00}(\omega) = 0$; thus there is definite interdependence between $I(X = 1)$ and $I(V \in \{1, 2\})$. The proof of the third part of the Proposition is similar. $\square$

Proof of Propositions 3, 4, 5 and 6. The proof of Proposition 4 is similar to that of Proposition 1. The proofs of Propositions 3, 5 and 6 are similar to that of Proposition 2. Details are available in the Supplementary Material. $\square$

Derivations for Tables 3 and 4. For binary and ternary exposures X and V , the first condition in Proposition 1 for $i = 1$ can be written in terms of model (5) as $e^{\beta_1}(e^{\beta_2+\beta_4} - 1) - (e^{\beta_2} - 1) > 0$. If $\beta_4 > 0$, this inequality holds since $e^{\beta_1} \geq 1$ by monotonicity. Derivations of the other conditions in Table 3 from Proposition 1 are similar. The first condition in Proposition 2 for $i = 1$ can be written as $e^{\beta_1}(\frac{1}{2}e^{\beta_2+\beta_4} - 1) + e^{\beta_2}(\frac{1}{2}e^{\beta_1+\beta_4} - 1) > 0$. If $\beta_4 > \log(2)$, this inequality holds provided $\beta_1 \geq 0$; note that $\beta_2 \geq 0$ by the monotonicity of V . Derivations of the other conditions in Table 3 from Propositions 2 and 3 are similar. Derivations for Table 4 are also similar. Details are available in the Supplementary Material.

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