

# The identification of synergism in the sufficient-component cause framework

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**Abstract.** Various concepts of interaction are reconsidered in light of a sufficient-component cause framework. Conditions and statistical tests are derived for the presence of synergism within sufficient causes. The conditions derived are sufficient but not necessary for the presence of synergism. In the context of monotonic effects, but not in general, the conditions which are derived are closely related but not identical to effect modification on the risk difference scale.

*Some Key Words:* Causal inference; effect modification; interaction; risk difference; sufficient-component cause; synergism.

The distinction between a biologic interaction or synergism and a statistical interaction has frequently been noted.<sup>1-3</sup> In the case of binary variables, concrete attempts have been made to articulate which types of counterfactual response patterns would constitute instances of interdependent effects.<sup>4-6</sup> In what follows we reconsider the definition of causal interdependence and its relation to that of synergism in light of the sufficient-component cause framework.<sup>7</sup> Consideration of this framework gives rise to a definition of "definite interdependence" which constitutes a sufficient but not necessary condition for the presence of synergism within the sufficient-component cause framework. We then derive various empirical conditions for the presence of synergism and provide a number of observations which illustrate the difference between the concepts of definite interdependence and effect modification on the risk difference scale. Although the material developed in this paper arguably has implications for applied data analysis, our principal aim here will be to extend theory: to consider various conceptual and mathematical relations between different notions of interaction.

## Synergism and Counterfactual Response Types

Suppose that  $D$  and two of its causes,  $E_1$  and  $E_2$ , are binary variables taking values 0 or 1. In the discussion that follows  $E_1$  and  $E_2$  are treated symmetrically so that  $E_1$  could be relabeled as  $E_2$  and  $E_2$  could be relabeled as  $E_1$ . We assume a deterministic counterfactual framework. Let  $D_{ij}(\omega)$  be the counterfactual value of  $D$  for individual  $\omega$  if  $E_1$  were set to  $i$  and  $E_2$  were set to  $j$ . Robins has shown that standard statistical summaries of uncertainty due to sampling variability, such as p-values and confidence intervals for proportions, have meaning in a deterministic model if and only if we regard (i) the  $n$  study subjects as having been randomly sampled from a large, perhaps hypothetical, source population of size  $N$ , such that  $n/N$  is very small and (ii) probability statements and expected values refer to proportions and averages in the source population.<sup>8</sup> Because we plan to discuss statistical tests, we adopt (i) and (ii). For event  $E$  we will denote the complement of the event by  $\bar{E}$ . The probability of an event  $E$  occurring,  $P(E = 1)$ , we will frequently simply denote by  $P(E)$ . If there were some individual  $\omega$  for whom  $D_{10}(\omega) = D_{01}(\omega) = D_{00}(\omega) = 0$  but for whom  $D_{11}(\omega) = 1$  we might say that there was synergism between the effect of  $E_1$  and  $E_2$  on  $D$  because in such a case there exists an individual for whom  $E_1$  or  $E_2$  alone is insufficient for  $D$  but for whom  $E_1$  and  $E_2$  together yield  $D$ . There is thus joint action between  $E_1$  and  $E_2$  and so we might speak of synergism. Similarly if there were individuals for whom  $D_{11}(\omega) = D_{01}(\omega) = D_{00}(\omega) = 0$  and  $D_{10}(\omega) = 1$ ; or for whom  $D_{11}(\omega) = D_{10}(\omega) = D_{00}(\omega) = 0$  and  $D_{01}(\omega) = 1$ ; or for whom  $D_{11}(\omega) = D_{01}(\omega) = D_{10}(\omega) = 0$  and  $D_{00}(\omega) = 1$  we might again

say that some form of synergism was present. In the first of these three additional cases, we might say there is synergism because only  $E_1$  and  $\overline{E_2}$  together imply  $D$ ; in the second case because only  $\overline{E_1}$  and  $E_2$  together imply  $D$ ; and in the third case because only  $\overline{E_1}$  and  $\overline{E_2}$  together imply  $D$ . We have considered four different response patterns which manifest some form of synergism. We will see below that these four response patterns and in fact two others are closely related to synergism within the sufficient-component cause framework.

Miettinen classified the various response patterns which arise from two binary causes,  $E_1$  and  $E_2$ , and a binary outcome  $D$  into sixteen different response types according to the individuals' counterfactual outcomes as enumerated in Table 1.<sup>4,5</sup>

Table 1. Enumeration of response patterns to four possible exposure combinations.

Type	$E_1 = 1, E_2 = 1$	$E_1 = 0, E_2 = 1$	$E_1 = 1, E_2 = 0$	$E_1 = 0, E_2 = 0$
1	1	1	1	1
2	1	1	1	0
3	1	1	0	1
4	1	1	0	0
5	1	0	1	1
6	1	0	1	0
7	1	0	0	1
8	1	0	0	0
9	0	1	1	1
10	0	1	1	0
11	0	1	0	1
12	0	1	0	0
13	0	0	1	1
14	0	0	1	0
15	0	0	0	1
16	0	0	0	0

Types 8, 10, 12, and 14 were classified by Miettinen as instances of causal interdependence. Types 3, 5, 7 and 9 were classified as instances of preventive interdependence. Miettinen thus included types 3, 5, 7, 8, 9, 10, 12, and 14 as those which constituted interdependent effects. Greenland and Poole criticized this classification because it was not invariant to interchanging the reference categories (i.e. relabeling for  $E_1$  or for  $E_2$  the label "1" as "0" and "0" as "1").<sup>6</sup> Type 15 for instance which is not classified as exhibiting causal interdependence in Miettinen's system would become a type 12 responder (which Miettinen did classify as exhibiting causal interdependence) if  $E_2 = 0$  were relabeled  $E_2 = 1$  and vice versa. Greenland and Poole therefore partitioned the types into equivalence classes which were invariant under the recoding of exposure indicators. Under the classification of Greenland and Poole, the equivalence class of types 7 and 10 is invariant and is said to exhibit mutual antagonism; the class composed of types 8, 12, 14 and 15 is invariant and consists of those types in which disease occurs for only one exposure combination; the class of types 2, 3, 5 and 9 is invariant and consists of those types in which disease occurs for exactly three exposure combinations. Under the classification of Greenland and Poole, these three classes constituting types 2, 3, 5, 7, 8, 9, 10, 12, 14 and 15 are all said to rep-

resent causal interdependence. Greenland and Poole note that if none of types 2, 3, 5, 7, 8, 9, 10, 12, 14 or 15 are present then the causal risk difference will be additive so that  $\mathbb{E}[D_{11}] - \mathbb{E}[D_{00}] = (\mathbb{E}[D_{10}] - \mathbb{E}[D_{00}]) + (\mathbb{E}[D_{01}] - \mathbb{E}[D_{00}])$  where  $\mathbb{E}$  denotes the average in the study population. For any individual of one of these types it is also the case that the effect of  $E_1$  on  $D$  cannot be determined without knowledge of the value of  $E_2$ . Later we will show, however, that Greenland and Poole's classification is insufficiently stringent for associating causal interdependence with synergism in the sufficient-component cause framework to which we now turn.

In the analysis that follows we will frequently use the disjunctive or OR operator,  $\vee$ , which is defined by  $a \vee b = a + b - ab$  and is such that  $a \vee b = 1$  if and only if either  $a = 1$  or  $b = 1$ . A conjunction or product of the events  $X_1, \dots, X_n$  will be written as  $X_1 \dots X_n$  so that  $X_1 \dots X_n = 1$  if and only if each of the the events  $X_1, \dots, X_n$  takes the value 1. Under the sufficient-component cause framework,<sup>7</sup> if  $S_1, \dots, S_n$  are all the sufficient causes for  $D$  then  $D = S_1 \vee \dots \vee S_n$  and each  $S_i$  is made up of some product of components,  $F_1^i, \dots, F_{m_i}^i$ , which are binary so that  $S_i = F_1^i \dots F_{m_i}^i$ . Following Rothman, we will say that two causes,  $E_1$  and  $E_2$ , for some outcome  $D$ , exhibit synergism if  $E_1$  and  $E_2$  are ever present together in the same sufficient cause.<sup>7,9</sup> If  $E_1$  and  $\overline{E_2}$  are present together in the same sufficient cause then the two causes  $\overline{E_1}$  and  $E_2$  are said to exhibit antagonism; in this case it could also be said that  $E_1$  and  $\overline{E_2}$  exhibit synergism. Note that  $E_1$  and  $E_2$  may exhibit both antagonism and synergism if, for example,  $E_1$  and  $E_2$  are present together in one sufficient cause and if  $E_1$  and  $\overline{E_2}$  are present together in another sufficient cause. In what follows we will not maintain the distinction between synergism and antagonism in so far as we will refer to a sufficient cause in which both  $E_1$  and  $\overline{E_2}$  are present as synergism between  $E_1$  and  $\overline{E_2}$  rather than as antagonism between  $E_1$  and  $E_2$ . It has become somewhat customary to refer to cases of synergism and antagonism in the sufficient-component cause framework as "biologic interactions."<sup>10-11</sup> This nomenclature, however, may not always be appropriate. Consider a recessive disease in which two mutant alleles convey the disease phenotype but one or zero copies of the mutant allele conveys the phenotype complement. Let  $E_1 = 1$  if the allele inherited from the mother is the mutant type and let  $E_2 = 1$  if the allele inherited from the father is the mutant type then  $E_1 E_2$  is a sufficient cause for the disease because if  $E_1 E_2 = 1$  then the disease will occur. Suppose that when both mutant types are present ( $E_1 E_2 = 1$ ) the disease occurs because neither allele allows for the production of an essential protein. Although there is synergism between  $E_1$  and  $E_2$  in the sufficient cause sense as both  $E_1 = 1$  and  $E_2 = 1$  are necessary for the disease, there is no *biological* sense in which the two alleles are interacting. In fact neither allele is involved in any activity at all and it is precisely this lack of action which brings about the disease. Thus, throughout this paper we will refrain from the use of the term "biologic interaction" and will instead refer to synergism within the sufficient-component cause framework. In contrast with "biologic interaction" which suggests that causes biologically act upon *each other* in bringing about the outcome, the term "synergism" suggests joint work on *the outcome* regardless of whether or not the causes act on one another.

There are certain correspondences between response types and sets of sufficient causes. Greenland and Poole, in the case of two binary causes, enumerate nine different sufficient causes each involving some combination of  $E_1$  and  $E_2$  and their complements along with certain binary background causes.<sup>6</sup> We may label these background causes as  $A_0, A_1, A_2$ ,

$A_3, A_4, A_5, A_6, A_7, A_8$ . The nine different sufficient causes Greenland and Poole give are then  $A_0, A_1E_1, A_2\overline{E_1}, A_3E_2, A_4\overline{E_2}, A_5E_1E_2, A_6\overline{E_1}E_2, A_7E_1\overline{E_2}$  and  $A_8\overline{E_1}\overline{E_2}$ . Note that in the case of the  $A_i$  and  $E_i$  variables, the subscript denotes which of the causes or background factors is being indicated whereas the subscripts for  $D_{ij}$  denote the counterfactual outcome with  $E_1$  set to  $i$  and  $E_2$  set to  $j$ . In many cases, not all of the nine sufficient causes will be present. Also, if one of the background causes is unnecessary for the  $D$  (i.e. some combination of  $E_1, E_2$  and their complements are alone sufficient for  $D$  for each member of the population) then the corresponding background cause  $A_i$  is equal to 1 for all subjects and we will in general suppress the  $A_i$ . Given the nine background causes, we thus have that

$$D = A_0 \vee A_1E_1 \vee A_2\overline{E_1} \vee A_3E_2 \vee A_4\overline{E_2} \vee A_5E_1E_2 \vee A_6\overline{E_1}E_2 \vee A_7E_1\overline{E_2} \vee A_8\overline{E_1}\overline{E_2}. \quad (1)$$

If one of  $A_5, A_6, A_7, A_8$  were non-zero, then we would say that  $E_1$  and  $E_2$  manifest a synergistic relationship. In what follows, we will assume that interventions on  $E_1$  and  $E_2$  do not affect any background causes  $A_i$ ; if they did then the  $A_i$  variable would be an *effect* of  $E_1$  and  $E_2$  rather than a *background* cause.<sup>12</sup> Furthermore, if one of the  $A_i$  variable were an effect of  $E_1$  and  $E_2$  then this could obscure the identification of synergistic relationships between  $E_1$  and  $E_2$ . For example, suppose that  $E_1$  and  $E_2$  together caused  $A_0$  so that  $A_0 = 1$  whenever  $E_1 = E_2 = 1$  and suppose that  $A_0$  was itself a sufficient cause for  $D$ . Then the  $A_0$  variable would essentially serve as a proxy for the synergism between  $E_1$  and  $E_2$ . We will thus require that none of the  $A_i$  variables are effects of  $E_1$  and  $E_2$ . It is in fact the case that it is always possible to construct the variables  $A_0, A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8$  so that none of the  $A_i$  variables are effects of  $E_1$  and  $E_2$  and so that equation (1) holds.<sup>13</sup>

Knowing whether there is a synergism between  $E_1$  and  $E_2$  will in general require having some knowledge of the causal mechanisms for the outcome  $D$ . For although a particular set of sufficient causes along with the presence or absence of the various background causes  $A_0, A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8$  for a particular individual suffices to fix a response type, the converse is not true.<sup>6,14</sup> That is to say, knowledge of an individual's response type does not generally fully determine which background causes are present. As an example, an individual who has  $A_1(\omega) = A_3(\omega) = 1$  and  $A_i(\omega) = 0$  for  $i \neq 1, 3$  has a sufficient cause completed if and only if  $E_1 = 1$  (in which case  $A_1E_1$  is completed) or  $E_2 = 1$  (in which case  $A_3E_2$  is completed). For such a individual we could write  $D = E_1 \vee E_2$ . Thus this individual would be of response type 2 because the individual will escape disease only if exposed to neither  $E_1$  nor  $E_2$  so that no sufficient cause is completed. In contrast, knowledge of a individual's response type does not generally fully determine which background causes are present. A individual who is of response type 2 could have either  $A_1(\omega) = A_3(\omega) = 1$  and  $A_i(\omega) = 0$  for  $i \neq 1, 3$  in which case we could write  $D = E_1 \vee E_2$  or alternatively such a individual may have  $A_5(\omega) = A_6(\omega) = A_7(\omega) = 1$  and  $A_i(\omega) = 0$  for  $i \neq 5, 6, 7$  in which case we could write  $D = E_1E_2 \vee \overline{E_1}E_2 \vee E_1\overline{E_2}$ . As noted by Greenland and Brumback, it is thus impossible in this case to distinguish from the counterfactual response pattern alone the set of sufficient causes  $E_1 \vee E_2$  from the set of sufficient causes  $E_1E_2 \vee \overline{E_1}E_2 \vee E_1\overline{E_2}$ .<sup>14</sup> With both sets of sufficient causes,  $D$  will occur when either  $E_1$  or  $E_2$  is present. Whether  $E_1 \vee E_2$  or  $E_1E_2 \vee \overline{E_1}E_2 \vee E_1\overline{E_2}$  represent the proper description of the causal mechanisms for  $D$  can only be resolved with knowledge of the subject matter in question.

Using the sufficient cause representation for  $D$  given above we can see that Greenland and Poole's classification of those types which represent causal interdependence is insufficiently stringent for associating causal interdependence with synergism within the sufficient-component cause framework. Greenland and Poole include types 2, 3, 5 and 9 amongst those types that are said to exhibit interdependent action. However, types 2, 3, 5 and 9 can in fact be observed even when  $D$  can be represented as  $D = A_0 \vee A_1 E_1 \vee A_2 \overline{E_1} \vee A_3 E_2 \vee A_4 \overline{E_2}$ . For example, if  $A_5 = A_6 = A_7 = A_8 = 0$  but if for some individual  $\omega$ ,  $A_0(\omega) = A_2(\omega) = A_4(\omega) = 0$  and  $A_1(\omega) = A_3(\omega) = 1$  so that  $D(\omega) = E_1 \vee E_2$  then, as seen above, this would give rise to response type 2. Similarly if  $A_0(\omega) = A_1(\omega) = A_4(\omega) = 0$  and  $A_2(\omega) = A_3(\omega) = 1$  then this would give rise to response type 3; if  $A_0(\omega) = A_2(\omega) = A_3(\omega) = 0$  and  $A_1(\omega) = A_4(\omega) = 1$  this would give rise to response type 5; if  $A_0(\omega) = A_1(\omega) = A_3(\omega) = 0$  and  $A_2(\omega) = A_4(\omega) = 1$  this would give rise to response type 9. Response types 2, 3, 5 and 9 might of course also arise from synergistic relationships. As noted above, response type 2 would arise if  $A_0(\omega) = A_1(\omega) = A_2(\omega) = A_3(\omega) = A_4(\omega) = A_5(\omega) = 0$  and  $A_5(\omega) = A_6(\omega) = A_7(\omega) = 1$ . Without further information concerning which causal mechanisms are present we cannot, in the case of types 2, 3, 5 and 9, ascertain from the counterfactual response patterns alone whether or not a synergism is manifest. The types that Greenland and Poole classify as not representing causal interdependence (types 1, 4, 6, 11, 13, 16) can, like types 2, 3, 5 and 9, also all be observed when  $D$  can be represented as  $D = A_0 \vee A_1 E_1 \vee A_2 \overline{E_1} \vee A_3 E_2 \vee A_4 \overline{E_2}$ . But all of these types, other than type 16, can also be observed when one or more of  $A_5, A_6, A_7, A_8$  are non-zero. In contrast, it can be shown that types 7, 8, 10, 12, 14, and 15 cannot be present when  $A_5 = A_6 = A_7 = A_8 = 0$ , i.e. when  $D = A_0 \vee A_1 E_1 \vee A_2 \overline{E_1} \vee A_3 E_2 \vee A_4 \overline{E_2}$ .<sup>13</sup> These six types thus clearly do constitute instances of synergism because one or more of  $A_5, A_6, A_7, A_8$  must be non-zero for such types to be present. Thus although synergistic relationships will sometimes be unidentified even when the counterfactual response patterns for all individuals are known, they will not always be unidentified. We will use the term "definite interdependence," which we make precise in Definition 1, to refer to a counterfactual response pattern which necessarily entails a synergistic relationship.

Note that  $D_{10}(\omega) = D_{01}(\omega) = 0$  and  $D_{11}(\omega) = 1$  if and only if individual  $\omega$  is of response type 7 or 8; also  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{01}(\omega) = 1$  if and only if individual  $\omega$  is of response type 10 or 12; also  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{10}(\omega) = 1$  if and only if individual  $\omega$  is of response type 10 or 14; and finally  $D_{01}(\omega) = D_{10}(\omega) = 0$  and  $D_{00}(\omega) = 1$  if and only if individual  $\omega$  is of response type 7 or 15. The presence of one of the six types that necessarily entail the presence of synergism is thus equivalent to the presence of an individual  $\omega$  for whom one of the following four conditions hold:  $D_{10}(\omega) = D_{01}(\omega) = 0$  and  $D_{11}(\omega) = 1$ ; or  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{01}(\omega) = 1$ ; or  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{10}(\omega) = 1$ ; or  $D_{01}(\omega) = D_{10}(\omega) = 0$  and  $D_{00}(\omega) = 1$ . Consequently, we define definite interdependence as follows.

**Definition 1 (Definite Interdependence).** Suppose that  $D$  and two of its causes,  $E_1$  and  $E_2$ , are binary. We say that there is definite interdependence between the effect of  $E_1$  and  $E_2$  on  $D$  if there exists an individual  $\omega$  for whom one of the following holds:  $D_{10}(\omega) = D_{01}(\omega) = 0$  and  $D_{11}(\omega) = 1$ ; or  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{01}(\omega) = 1$ ; or  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{10}(\omega) = 1$ ; or  $D_{01}(\omega) = D_{10}(\omega) = 0$  and  $D_{00}(\omega) = 1$ .

Figure 1. Implications amongst different concepts of interaction.

Effect Modification of the Risk Difference: The expected causal risk difference of  $E_1$  on  $D$  varies within strata of  $E_2$

Causal Interdependence: The presence of a response type for whom the effect of  $E_1$  on  $D$  cannot be determined without knowledge of  $E_2$

Definite Interdependence: Every sufficient cause representation for  $D$  must have a sufficient cause in which  $E_1$  and  $E_2$  are both present

Synergism: The sufficient cause representation for  $D$  that corresponds to the actual causal mechanisms for  $D$  has a sufficient cause in which  $E_1$  and  $E_2$  are both present

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Synergism: The sufficient cause representation for  $D$  that corresponds to the actual causal mechanisms for  $D$  has a sufficient cause in which  $E_1$  and  $E_2$  are both present. The definition of definite interdependence is equivalent to the presence within a population of an individual with a counterfactual response pattern of type 7, 8, 10, 12, 14, or 15. As defined above, if  $E_1$  and  $E_2$  exhibit definite interdependence then there must be synergism between  $E_1$  and  $E_2$ . If  $D_{10}(\omega) = D_{01}(\omega) = 0$  and  $D_{11}(\omega) = 1$  then  $A_5 \neq 0$  and there will be synergism between  $E_1$  and  $E_2$ . If  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{01}(\omega) = 1$  then  $A_6 \neq 0$  and there will be synergism between  $\overline{E_1}$  and  $E_2$ . If  $D_{11}(\omega) = D_{00}(\omega) = 0$  and  $D_{10}(\omega) = 1$  then  $A_7 \neq 0$  and there will be synergism between  $E_1$  and  $\overline{E_2}$ . If  $D_{01}(\omega) = D_{10}(\omega) = 0$  and  $D_{00}(\omega) = 1$  then  $A_8 \neq 0$  and there will be synergism between  $\overline{E_1}$  and  $\overline{E_2}$ . As made clear in the discussion above, however, although definite interdependence is sufficient for a synergistic relationship, it is not necessary. There may be synergism between  $E_1$  and  $E_2$  even if they do not exhibit definite interdependence. Several related concepts have been considered. In Figure 1 we give a diagram indicating the implications amongst these different concepts.

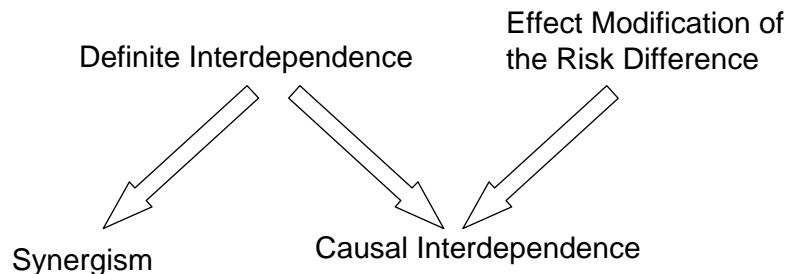


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Synergism: The sufficient cause representation for  $D$  that corresponds to the actual causal mechanisms for  $D$  has a sufficient cause in which  $E_1$  and  $E_2$  are both present

First, as noted by Greenland and Poole, effect modification on the risk difference scale implies causal interdependence.<sup>6</sup> Second, definite interdependence implies both causal interdependence (because types 7, 8, 10, 12, 14 and 15 are a subset of types 2, 3, 5, 7, 8, 9, 10,

12, 14 and 15) and the presence of synergism.<sup>13</sup> No other implications amongst these four concepts hold.

Two additional comments with regard to definite interdependence are worth noting. First, Greenland and Poole note that there is a one-to-one correspondence between response types 8, 12, 14 and 15 and "cause types" corresponding to  $A_5(\omega) = 1$ ,  $A_6(\omega) = 1$ ,  $A_7(\omega) = 1$  and  $A_8(\omega) = 1$  respectively with all other  $A_i(\omega) = 0$ .<sup>6</sup> They also note that response type 16 arises if and only if  $A_i(\omega) = 0$  for all  $i$ . However, they claim that there are no other one-to-one correspondences for the remaining 11 response types. They failed to notice that response type 7 arises if and only if  $A_5(\omega) = 1$  and  $A_8(\omega) = 1$  with  $A_i(\omega) = 0$  for all  $i \notin \{5, 8\}$  and that response type 10 arises if and only if  $A_6(\omega) = 1$  and  $A_7(\omega) = 1$  with  $A_i(\omega) = 0$  for all  $i \notin \{6, 7\}$ . We will see below that this insight that response types 7 and 10 necessarily entail a synergistic relationship is important in constructing statistical tests for the presence of synergism.

Second, the definition of definite interdependence given above is invariant to the relabeling of the levels of  $E_1$  and  $E_2$  i.e. relabeling for  $E_1$  and/or for  $E_2$  the level "1" as "0" and "0" as "1." Definite interdependence as defined above is not, however, invariant to the relabeling of the levels of  $D$ . If  $D$  is relabeled so that "1" is "0" and "0" is "1" then types 8, 12, 14, and 15 become types 9, 5, 3, and 2 respectively and these latter types do not exhibit definite interdependence. The sufficient-component cause framework (along with its philosophical counterpart)<sup>15</sup> assumes that there is an asymmetry between the event and its complement in there is a particular event or state that needs explaining. It is the event, not its complement, that requires an explanation. For example, let  $D$  denote death, let  $E_1$  denote the presence of a gene that gives rise to a peanut allergy and let  $E_2$  denote exposure to peanuts so that if both  $E_1$  and  $E_2$  are present the individual will die. The event we seek to explain is death. Suppose that the lethal allergic reaction to peanuts is the only cause of death in a particular time horizon. In this case we would represent the sufficient causes for death by  $D = E_1 E_2$  and since  $E_1$  and  $E_2$  are present together in the same sufficient cause we would say that  $E_1$  and  $E_2$  manifest synergism. If, however, we were considering the outcome of survival,  $\overline{D}$ , then either  $\overline{E_1}$  or  $\overline{E_2}$  would be sufficient for averting death and the sufficient causes for not dying would be represented by  $\overline{D} = \overline{E_1} \vee \overline{E_2}$  and no synergism between  $\overline{E_1}$  and  $\overline{E_2}$  would be thought to be present. We seen then that the presence of synergism for an outcome does not imply the presence of synergism for the complement of that outcome. In the example just considered, however, it is death not survival that requires explanation and so it is synergism for the event of death that will be of interest.

## Testing for Synergism in the Sufficient-Component Cause Framework

When there is no confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  or if there exists a set of variables  $C$  such that conditioning on  $C$  suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  then it is possible to develop statistical tests for the presence of synergism. Theorem 1 gives a condition which is sufficient for the presence of synergism and which with data can be statistically tested. The proof of Theorem 1 and that of Theorem 2 below are given in Appendix 1. We will say that  $C$  suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  if the counterfactual variables  $D_{ij}$  are conditionally independent of  $(E_1, E_2)$  given  $C$ . If this condition holds then

$$P(D_{ij} = 1|C = c) = P(D = 1|E_1 = i, E_2 = j, C = c).$$

Theorem 1. Suppose that  $D$  and two of its causes,  $E_1$  and  $E_2$ , are binary. Let  $C$  be a set of variables that suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  then if for any value  $c$  of  $C$  we have that  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) > 0$  then there is synergism between  $E_1$  and  $E_2$ .

When the condition of Theorem 1 is met, an individual of either type 7 or type 8 must be present and from the discussion above it follows that there must be synergism between  $E_1$  and  $E_2$ . Theorem 1 has analogues for testing for synergism between  $E_1$  and  $\overline{E_2}$  or between  $\overline{E_1}$  and  $E_2$  or between  $\overline{E_1}$  and  $\overline{E_2}$ . If for some  $c$ ,  $P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c) > 0$  then an individual of type 10 or type 14 must be present and there will be synergism between  $E_1$  and  $\overline{E_2}$ . If  $P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c) > 0$  then an individual of type 10 or type 12 must be present and there will be synergism between  $\overline{E_1}$  and  $E_2$ . If  $P(D = 1|E_1 = 0, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) > 0$  then an individual of type 7 or type 15 must be present and there will be synergism between  $\overline{E_1}$  and  $\overline{E_2}$ . Theorem 1 and its analogues demonstrate that the claim of Rothman and Greenland that "inferences about the presence of particular response types or sufficient causes must depend on very restrictive assumptions about absence of other response types" (p. 339) is false.<sup>11</sup> Although their claim holds for inference about particular response types, Theorem 1 demonstrates that it does not hold for inferences about sufficient causes. Theorem 1 makes no assumption about the absence of any response type.

It is interesting to note that Theorem 1 does not make reference to probability of the outcome  $D$  when  $E_1$  and  $E_2$  are both 0 i.e. to  $P(D = 1|E_1 = 0, E_2 = 0, C = c)$ . The condition of Theorem 1 essentially ensures the presence of some individual  $\omega$  for whom  $D_{11}(\omega) = 1$  and for whom  $D_{10}(\omega) = D_{01}(\omega) = 0$ . For such an individual, if  $D_{00}(\omega) = 0$  then individual  $\omega$  is of type 8; if  $D_{00}(\omega) = 1$  then individual  $\omega$  is of type 7. Theorem 1 does not distinguish between types 7 and 8; the conclusion of the theorem simply implies that an individual of one of these two types must be present and thus that there must be synergism between  $E_1$  and  $E_2$ . Whether individual is  $\omega$  of type 7 or type 8 will affect the probability  $P(D = 1|E_1 = 0, E_2 = 0, C = c)$  but it will not affect the probability involved in the condition given in Theorem 1, namely  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c)$ .

We consider an example concerning the effects of smoking and asbestos on lung cancer. For the purpose of this example we will ignore sampling variability. Suppose that the rate ratios for lung cancer given smoking status  $S$  and asbestos exposure  $A$  are given in Table 2. Let  $R_{ij}$  be the risk (i.e. cumulative incidence) of lung cancer before age 60 if smoking status  $S$  is  $i$  and asbestos exposure  $A$  is  $j$  and let  $RR_{ij}$  be the relative risk of lung cancer before age 60 for individuals with  $S = i$  and  $A = j$  as compared to lung cancer risk for individuals unexposed to smoking and asbestos. Since in all smoking-asbestos categories the risk of lung cancer before age 60 is small, the risk ratio  $RR_{ij}$  closely approximates the rate ratios in Table 2.

Table 2. Rate ratios of lung cancer for smoking and asbestos exposure.

	A=0	A=1
S=0	1	3
S=1	10	30

S denotes smoking status

A denotes asbestos exposure

Suppose that the data is unconfounded by other factors so that  $R_{ij} = P(D = 1|S = i, A = j)$ . The condition of Theorem 1 may be written as  $R_{11} - R_{01} - R_{10} > 0$ . By dividing this condition by  $R_{00}$  the condition can be re-written as  $RR_{11} - RR_{01} - RR_{10} > 0$ . In this case,  $RR_{11} - RR_{01} - RR_{10} = 30 - 3 - 10 = 17 > 0$ . We could thus conclude that synergism was present in the sufficient cause sense between smoking and asbestos exposure. Note that the conclusion of the presence of synergism in the sufficient cause sense holds in spite of the fact that the multiplicative risk model holds i.e.  $RR_{11} = RR_{01}RR_{10}$ . Note further that the conclusion of the presence of synergism in the sufficient cause sense did *not* preclude cases in which one or both factors are sometimes preventive. For example, for certain individuals exposure to asbestos might protect against lung cancer. This might be the case if (i) there exist individuals who carry a very low risk of smoking induced cancer due to a genetic polymorphism but who still suffer from smoking-induced chronic bronchitis and (ii) the narrowed airways and increased mucous caused by their bronchitis trap and eliminate asbestos fibers that would have otherwise reached the lung parenchyma. Theorem 1 can still be applied to such cases. The example of course is rather simplified in that smoking and asbestos exposure are better captured by continuous rather than binary measures. The difficulties which continuous variables pose to the sufficient-component cause framework is taken up in the discussion section. Also, in practice, with finite samples, one must use various statistical tests and methods of statistical inference in order to determine whether the condition given in Theorem 1 holds. One such statistical test is given in Appendix 2. Such tests can be used empirically with epidemiologic data to test for synergism in the sufficient-component cause framework. Limitations of such tests are discussed at the paper's conclusion.

## Testing for Synergism under the Assumption of Monotonic Effects

We next consider a context in which the direction of the effect (positive or negative) that  $E_1$  and  $E_2$  have on  $D$  is known. We make these ideas precise by introducing the concept of a monotonic effect. Considerable intuition regarding synergism can be garnered by the consideration of the setting of monotonic effects. Furthermore, as will be seen shortly, the setting of monotonic effects also allows for the construction of more powerful tests for detecting synergism than is possible without the assumption.

**Definition 2 (Monotonic Effect):** We will say that  $E_1$  has a positive monotonic effect on  $D$  if for all individuals  $\omega$  we have  $D_{ij}(\omega) \geq D_{i'j}(\omega)$  whenever  $i \geq i'$ ; we will say that  $E_2$  has a positive monotonic effect on  $D$  if for all individuals  $\omega$  we have  $D_{ij}(\omega) \geq D_{ij'}(\omega)$  whenever  $j \geq j'$ . Similarly, we will say that  $E_1$  has a negative monotonic effect on  $D$  if for all individuals  $\omega$  we have  $D_{ij}(\omega) \leq D_{i'j}(\omega)$  whenever  $i \geq i'$  and that  $E_2$  has a negative monotonic effect on  $D$  if for all individuals  $\omega$  we have  $D_{ij}(\omega) \leq D_{ij'}(\omega)$  whenever  $j \geq j'$ .

The definition of a monotonic effect essentially requires that some intervention either increase or decrease some other variable  $D$  not merely on average over the entire population but rather for every individual in that population regardless of the other intervention. The requirements for the attribution of a monotonic effect are thus considerable. However whenever a particular intervention is always beneficial or neutral for all individuals, there is a positive monotonic effect; whenever the intervention is always harmful or neutral for all individuals, there is a negative monotonic effect. The assumption of monotonic effects has been used elsewhere in the context of concepts of interaction,<sup>9,11,12,16</sup> and it is sometimes referred to as an assumption of "no preventive effects" or purely "causative factors." It can be shown that  $E_1$  has a positive monotonic effect on  $D$  if and only if  $\overline{E_1}$  is not present in any sufficient cause. Similarly,  $E_1$  has a negative monotonic effect on  $D$  if and only if  $E_1$  is not present in any sufficient cause (though  $\overline{E_1}$  may still be present).

Theorem 2 gives a result similar to that of Theorem 1 but under the assumption that both  $E_1$  and  $E_2$  have positive monotonic effects on  $D$ .

**Theorem 2.** Suppose that  $D$  and two of its causes,  $E_1$  and  $E_2$ , are binary and that  $E_1$  and  $E_2$  have a positive monotonic effect on  $D$ . Let  $C$  be a set of variables that suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  then if for any value  $c$  of  $C$  we have that  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) > P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  then there is synergism between  $E_1$  and  $E_2$ .

The condition provided in Theorem 2 has obvious analogues if one or both of  $E_1$  and  $E_2$  are replaced by  $\overline{E_1}$  and  $\overline{E_2}$  respectively and if one or both of  $E_1$  and  $E_2$  have a negative monotonic effect rather than a positive monotonic effect on  $D$ . If the condition of Theorem 2 is met, an individual of type 8 must be present. Individuals of type 7, the other type that entails synergism between  $E_1$  and  $E_2$ , are precluded because  $E_1$  has a positive monotonic effect on  $D$  (and similarly because  $E_2$  has a positive monotonic effect on  $D$ ). Rothman and Greenland note the equivalent result in the setting of no confounding factors.<sup>11</sup> A statistical test for the condition of Theorem 2 is given in Appendix 2. As noted above, such tests can be used empirically with epidemiologic data to test for synergism in the sufficient-component cause framework. Note that the general condition of Theorem 1 for detecting the presence of synergism between  $E_1$  and  $E_2$ ,  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) > 0$ , is stronger than the condition,  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) + P(D = 1|E_1 = 0, E_2 = 0, C = c) > 0$ , required in the setting of monotonic effects. Indeed the former clearly implies the latter. The statistical tests based on this condition in the setting of monotonic effects will thus be more powerful than the equivalent tests in the general setting.

## Effect Modification and Synergism

Theorem 2 suggests the risk difference scale as the means by which to test for synergism in the presence of monotonic effects. As will be seen below and as has been pointed out before, effect modification on the risk difference scale need not imply any form of synergy. Furthermore, in the presence of confounding, effect modification on the risk difference scale

need not even imply the modification of an actual causal *effect*. Nevertheless, Theorem 2 can be interpreted as stating that, conditional on confounding factors, if the risk difference for  $E_1$  in the strata  $E_2 = 1$  is greater than the risk difference for  $E_1$  in the strata  $E_2 = 0$  then  $E_1$  and  $E_2$  must exhibit synergism. The condition can also be re-written as  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c) > \{P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)\} + \{P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)\}$  i.e. the effect of  $E_1$  and  $E_2$  is greater than the sum of the effects of  $E_1$  and  $E_2$  separately. The result is in many ways intuitive and not at all surprising. Nevertheless, several distinctions between the categories of effect modification on the risk difference scale and that of definite interdependence or synergism must be kept in mind however. We give numerical examples in Appendix 3 to demonstrate the following observations. First, it is possible to have effect modification on the risk difference scale without the presence of synergism in the sufficient-component cause framework (see Appendix 3, Numerical Example 1). This may arise when the effect modification is in the opposite direction of that required by Theorem 2.

Second, it is furthermore the case that the absence of effect modification on the risk difference scale does not imply the absence of synergism. In other words, if  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) > P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  then there must be synergism but even if  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) \leq P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  there may yet be a synergistic relationship (see Appendix 3, Numerical Example 2). Thus, Theorem 2 gives a condition (in terms of effect modification on the risk difference scale) which, in the setting of monotonic effects, is sufficient for synergism but not necessary. Third, if it is not the case that both  $E_1$  and  $E_2$  have a monotonic effect on  $D$  then we may have  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) > P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0)$  even when there is no synergism and furthermore in such cases we can also have  $E_2$  acting as a qualitative effect modifier for the risk difference of  $E_1$  on  $D$  without  $E_1$  and  $E_2$  manifesting synergism (see Appendix 3, Numerical Example 3).

These comments and the three numerical examples in the Appendix thus help clarify the conceptual distinction between effect modification on the risk difference scale and synergism, even in the presence of monotonic effects. There can be effect modification on the risk difference scale without the presence of synergism. There can be synergism without the risk difference condition  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) > P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  holding. And, finally, outside the context of monotonic effects, we may have  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) > P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  without the presence of synergism.

## Discussion

The present work has extended the literature on the relationship between counterfactual response types and the concept of synergism in the sufficient-component cause framework. The paper contributes substantially to the conceptual literature on synergism and provides novel tests for detecting synergistic relationships. The specific contributions of the paper are

as follows. First, we have provided a complete characterization, in the context of two binary causes, of those response types that necessarily entail synergism in the sufficient-component cause framework; the collection of these response types we have given the label "definite interdependence." Second, this characterization has allowed for the derivation of empirical conditions which, under the assumption of no unmeasured confounders, necessarily entail the presence of synergism (Theorems 1 and 2). Theorem 2, in the context of monotonic effects, is a straightforward generalization of previous results in the literature. However, Theorem 1, which makes no assumptions about the absence of certain response types, is entirely novel. These results can be used to empirically test for synergism in the sufficient-component cause framework. Third, we have illustrated through a series of numerical examples in Appendix 3 the distinction between the concept of effect modification on the risk difference scale and the conditions which necessarily entail the presence of synergism.

Several issues merit further attention. First, it is to be noted that the sufficient-component cause framework is limited in an important respect: it is restricted to binary variables (or variables that can be re-coded as binary variables). Thus in biologic systems governing continuous variables the concept of synergism arising from the sufficient-component cause framework is not applicable. Note that it has also been pointed out that with continuous variables it furthermore becomes difficult to separate assumptions about interaction from those of induction time and dose-response.<sup>17-18</sup> Second, the tests for synergism could be extended to the case of three or more variables. We have addressed this extension in related research.<sup>13</sup> Third, the discussion in the paper has assumed a *deterministic* counterfactual and sufficient-component cause setting. Relationships between a stochastic counterfactual setting (wherein each individual has a certain probability of disease under each of the four exposure combinations) and stochastic sufficient causes (wherein when a sufficient cause is completed, the individual has a certain probability of the outcome) could also be considered. Finally, our focus has been conceptual, with relatively little attention given to applied data analysis. It has been noted elsewhere that the power for tests of interaction are often low in many study settings.<sup>19</sup> Further work remains to be done in examining whether the statistical tests derived in this paper could be usefully employed in actual studies. Recent studies in genetics with regard to gene-gene and gene-environment interactions might be a fruitful area in which to examine the potential utility of these tests.

## Appendix 1. Proofs.

### *Proof of Theorem 1.*

Suppose that for some set of variables  $V$ ,  $\mathbb{E}[D_{11} - D_{01} - D_{10}|V = v] > 0$  then there must be some individual  $\omega$  for whom  $V = v$  and  $D_{11}(\omega) = 1$  but  $D_{01}(\omega) = D_{10}(\omega) = 0$  for if one of  $D_{01}(\omega), D_{10}(\omega)$  were always 1 whenever  $D_{11}(\omega) = 1$  then  $D_{11}(\omega) - D_{01}(\omega) - D_{10}(\omega)$  would be less than or equal to zero for all  $\omega$  and so we would have that  $\mathbb{E}[D_{11} - D_{01} - D_{10}|V = v] \leq 0$ . Let  $V = C$ . The condition  $\mathbb{E}[D_{11} - D_{01} - D_{10}|C = c] > 0$  implies definite interdependence and thus the presence of synergism. Because  $C$  is a set of variables that suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  we have that the counterfactual variables  $D_{ij}$  are conditionally independent of  $(E_1, E_2)$  given  $C$ . Thus we have,  $\mathbb{E}[D_{11} - D_{01} - D_{10}|C = c] = \mathbb{E}[D_{11}|E_1 = 1, E_2 = 1, C = c] - \mathbb{E}[D_{01}|E_1 = 0, E_2 = 1, C =$

$c] - \mathbb{E}[D_{10}|E_1 = 1, E_2 = 0, C = c] = P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c)$ . Consequently, if  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) > 0$  then  $E_1$  and  $E_2$  must exhibit synergism.

*Proof of Theorem 2.*

We first show that if for some set of variables  $V$ ,  $\mathbb{E}[(D_{11} - D_{01}) - (D_{10} - D_{00})|V = v] > 0$  for some  $v$  then there must be synergism. For each individual  $\omega$  define  $B_0(\omega)$ ,  $B_1(\omega)$ ,  $B_2(\omega)$  and  $B_3(\omega)$  as follows:  $B_0(\omega) = 1$  if  $D_{00}(\omega) = 1$  and 0 otherwise;  $B_1(\omega) = 1$  if  $D_{10}(\omega) = 1$  and 0 otherwise;  $B_2(\omega) = 1$  if  $D_{01}(\omega) = 1$  and 0 otherwise; and  $B_3(\omega) = 1$  if  $D_{11}(\omega) = 1$  and  $D_{10}(\omega) = D_{01}(\omega) = 0$  and 0 otherwise. Then  $D_{00} = B_0$ ,  $D_{10} = B_0 \vee B_1$ ,  $D_{01} = B_0 \vee B_2$ ,  $D_{11} = B_0 \vee B_1 \vee B_2 \vee B_3$ . Suppose there is no synergism between  $E_1$  and  $E_2$ ; then  $B_3(\omega) = 0$  for all  $\omega \in \Omega$  so that  $D_{11} = B_0 \vee B_1 \vee B_2$ . Let  $P(B_0|V = v) = b_0^v$ ,  $P(B_1|V = v) = b_1^v$ ,  $P(B_2|V = v) = b_2^v$ ,  $P(B_0B_1|V = v) = b_{01}^v$ ,  $P(B_0B_2|V = v) = b_{02}^v$ ,  $P(B_1B_2|V = v) = b_{12}^v$  and  $P(B_0B_1B_2|V = v) = b_{012}^v$ . Then  $P(B_0|V = v) = b_0^v$ ;  $P(B_0 \vee B_1|V = v) = b_0^v + b_1^v - b_{01}^v$ ;  $P(B_0 \vee B_2|V = v) = b_0^v + b_2^v - b_{02}^v$ ;  $P(B_0 \vee B_1 \vee B_2|V = v) = b_0^v + b_1^v + b_2^v - (b_{01}^v + b_{02}^v + b_{12}^v) + b_{012}^v$ .  $\mathbb{E}[(D_{11} - D_{01}) - (D_{10} - D_{00})|V = v] = \{P(B_0 \vee B_1 \vee B_2|V = v) - P(B_0 \vee B_2|V = v)\} - \{P(B_0 \vee B_1|V = v) - P(B_0|V = v)\} = [\{b_0^v + b_1^v + b_2^v - (b_{01}^v + b_{02}^v + b_{12}^v) + b_{012}^v\} - \{b_0^v + b_2^v - b_{02}^v\}] - [\{b_0^v + b_1^v - b_{01}^v\} - b_0^v] = (b_{012}^v - b_{12}^v + b_1^v - b_{01}^v) - (b_1^v - b_{01}^v) = b_{012}^v - b_{12}^v < 0$ . Thus if  $\mathbb{E}[(D_{11} - D_{01}) - (D_{10} - D_{00})|V = v] > 0$  we cannot have  $B_3(\omega) = 0$  for all  $\omega$  and so there must be synergism between  $E_1$  and  $E_2$ . Now let  $V = C$  then we have that synergism is implied by the condition  $\mathbb{E}[(D_{11} - D_{01}) - (D_{10} - D_{00})|C = c] > 0$ . Because  $C$  is a set of variables that suffices to control for the confounding of the causal effects of  $E_1$  and  $E_2$  on  $D$  we have that the counterfactual variables  $D_{ij}$  are conditionally independent of  $(E_1, E_2)$  given  $C$  and so we have,  $\mathbb{E}[(D_{11} - D_{01}) - (D_{10} - D_{00})|C = c] = \{\mathbb{E}[D_{11}|C = c] - \mathbb{E}[D_{01}|C = c]\} - \{\mathbb{E}[D_{10}|C = c] - \mathbb{E}[D_{00}|C = c]\} = \{\mathbb{E}[D_{11}|E_1 = 1, E_2 = 1, C = c] - \mathbb{E}[D_{01}|E_1 = 0, E_2 = 1, C = c]\} - \{\mathbb{E}[D_{10}|E_1 = 1, E_2 = 0, C = c] - \mathbb{E}[D_{00}|E_1 = 0, E_2 = 0, C = c]\} = \{P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c)\} - \{P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)\}$ . Thus if  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) > P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  then  $E_1$  and  $E_2$  must exhibit synergism.

## Appendix 2. Statistical Tests.

In this Appendix we develop statistical tests related to Theorems 1 and 2. For Theorem 1, to test the null that  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) \leq 0$  for a particular sample one may let  $n_{ij}$  denote the number of individuals in stratum  $C = c$  with  $E_1 = i$  and  $E_2 = j$  and let  $d_{ij}$  denote the number of individuals in stratum  $C = c$  with  $E_1 = i$ ,  $E_2 = j$  and  $D = 1$  then tests of the null hypothesis  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) \leq 0$  can be constructed using critical regions of the following form:  $\left\{ \frac{\left( \frac{d_{11} - d_{01} - d_{10}}{n_{11} - n_{01} - n_{10}} \right)}{\sqrt{\frac{d_{11}(n_{11} - d_{11}) + d_{01}(n_{01} - d_{01}) + d_{10}(n_{10} - d_{10})}{n_{11}^3} + \frac{d_{01}(n_{01} - d_{01})}{n_{01}^3} + \frac{d_{10}(n_{10} - d_{10})}{n_{10}^3}}} \right\} > Z_{1-\alpha}$ , to carry out a one-sided (upper tail) test. This can be seen by letting  $p_{ij}$  denote the true probability of  $D = 1$  conditional on  $E_1 = i$ ,  $E_2 = j$  and  $C = c$ . The hypothesis  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D =$

$1|E_1 = 0, E_2 = 1, C = c) - P(D = 1|E_1 = 1, E_2 = 0, C = c) \leq 0$  is that  $(p_{11} - p_{01} - p_{10}) \leq 0$ . We have that  $d_{ij} \sim \text{Bin}(n_{ij}, p_{ij})$  with  $\mathbb{E}[\frac{d_{ij}}{n_{ij}}] = p_{ij}$  and  $\text{Var}(\frac{d_{ij}}{n_{ij}}) = \frac{p_{ij}(1-p_{ij})}{n_{ij}}$ . By the

central limit theorem  $\frac{(\frac{d_{11}}{n_{11}} - \frac{d_{01}}{n_{01}} - \frac{d_{10}}{n_{10}}) - (p_{11} - p_{01} - p_{10})}{\sqrt{\frac{p_{11}(1-p_{11})}{n_{11}} + \frac{p_{01}(1-p_{01})}{n_{01}} + \frac{p_{10}(1-p_{10})}{n_{10}}}} \sim N(0, 1)$  and by Slutsky's

theorem we have  $\frac{(\frac{d_{11}}{n_{11}} - \frac{d_{01}}{n_{01}} - \frac{d_{10}}{n_{10}}) - (p_{11} - p_{01} - p_{10})}{\sqrt{\frac{d_{11}(n_{11}-d_{11})}{n_{11}^3} + \frac{d_{01}(n_{01}-d_{01})}{n_{01}^3} + \frac{d_{10}(n_{10}-d_{10})}{n_{10}^3}}} \sim N(0, 1)$ . To test the hypothesis  $H_0$ :

$(p_{11} - p_{01} - p_{10}) \leq 0$  vs.  $H_A$ :  $(p_{11} - p_{01} - p_{10}) > 0$  one may thus use the test statistic:

$$\frac{(\frac{d_{11}}{n_{11}} - \frac{d_{01}}{n_{01}} - \frac{d_{10}}{n_{10}})}{\sqrt{\frac{d_{11}(n_{11}-d_{11})}{n_{11}^3} + \frac{d_{01}(n_{01}-d_{01})}{n_{01}^3} + \frac{d_{10}(n_{10}-d_{10})}{n_{10}^3}}}.$$

If  $C$  consists of a small number of binary or categorical variables then it may be possible to use the tests constructed above to test all strata of  $C$ . When  $C$  includes a continuous variable or many binary and categorical variables such testing becomes difficult because the data in certain strata of  $C$  will be sparse. One might then model the conditional probabilities  $P(D = 1|E_1, E_2, C)$  using a binomial or Poisson regression model with a linear link.<sup>20–24</sup> For case-control studies it will be necessary to use an adapted set of modeling techniques.<sup>23,25,26</sup>

The condition of Theorem 2 can be tested in a manner analogous to the condition of Theorem 1. In general to test the null that  $P(D = 1|E_1 = 1, E_2 = 1, C = c) - P(D = 1|E_1 = 0, E_2 = 1, C = c) \leq P(D = 1|E_1 = 1, E_2 = 0, C = c) - P(D = 1|E_1 = 0, E_2 = 0, C = c)$  for a particular sample, tests of the null hypothesis can be constructed using critical regions of

the following form:  $\left\{ \frac{(\frac{d_{11}}{n_{11}} - \frac{d_{01}}{n_{01}}) - (\frac{d_{10}}{n_{10}} - \frac{d_{00}}{n_{00}})}{\sqrt{\frac{d_{11}(n_{11}-d_{11})}{n_{11}^3} + \frac{d_{01}(n_{01}-d_{01})}{n_{01}^3} + \frac{d_{10}(n_{10}-d_{10})}{n_{10}^3} + \frac{d_{00}(n_{00}-d_{00})}{n_{00}^3}}} > Z_{1-\alpha} \right\}$ .

### Appendix 3. Numerical Examples for Effect Modification, Definite Interdependence and the Multiplicative Survival Model.

This appendix presents three computational examples illustrating the difference between effect modification on the risk difference scale and the concepts of definite interdependence and synergism. Recall, effect modification on the risk difference scale is said to be present if  $P(D = 1|E_1 = 1, E_2 = e_2) - P(D = 1|E_1 = 0, E_2 = e_2)$  varies with the value of  $e_2$ . In the absence of confounding this is also equal to the causal risk difference  $\mathbb{E}(D_{1e_2}) - \mathbb{E}(D_{0e_2})$ . Definite interdependence between  $E_1$  and  $E_2$  is said to be manifest if every sufficient cause representation for  $D$  must have a sufficient cause in which both  $E_1$  and  $E_2$  (or one or both their complements) are present. There is said to be synergism between  $E_1$  and  $E_2$  if the sufficient cause representation that corresponds to the actual causal mechanisms for  $D$  has a sufficient cause in which both  $E_1$  and  $E_2$  are present.

Numerical Example 1. We show that effect modification of the risk difference may be present without definite interdependence or synergism. Suppose that  $D$ ,  $E_1$  and  $E_2$  are binary and that  $D = A_0 \vee A_1 E_1 \vee A_2 E_2$ . Then  $E_1$  and  $E_2$  have a positive monotonic effect on  $D$  and  $E_1$  and  $E_2$  do not exhibit definite interdependence. Suppose further that the causal effects of  $E_1$  and  $E_2$  on  $D$  are unconfounded. Let  $P(A_0) = a_0, P(A_1) = a_1, P(A_2) = a_2, P(A_0 A_1) = a_{01}, P(A_0 A_2) = a_{02}, P(A_1 A_2) = a_{12}, P(A_0 A_1 A_2) = a_{012}$ . We then have  $P(D = 1|E_1 = 0, E_2 = 0) = P(A_0) = a_0$ ;  $P(D = 1|E_1 = 1, E_2 = 0) = P(A_0 \vee A_1) = a_0 + a_1 - a_{01}$ ;  $P(D = 1|E_1 = 0, E_2 = 1) = P(A_0 \vee A_2) = a_0 + a_2 - a_{02}$ ; and  $P(D =$

$1|E_1 = 1, E_2 = 1) = P(A_0 \vee A_1 \vee A_2) = a_0 + a_1 + a_2 - a_{01} - a_{02} - a_{12} + a_{012}$ . Conditional on  $E_2 = 0$ , the risk difference for  $E_1$  is given by:  $P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0) = a_0 + a_1 - a_{01} - a_0 = a_1 - a_{01}$ . Conditional on  $E_2 = 1$ , the risk difference for  $E_1$  is given by:  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) = a_0 + a_1 + a_2 - a_{01} - a_{02} - a_{12} + a_{012} - (a_0 + a_2 - a_{02}) = (a_1 - a_{01}) - (a_{12} - a_{012})$ . In this example,  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) = (a_1 - a_{01}) - (a_{12} - a_{012}) \neq a_1 - a_{01} = P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0)$ . We see then from this example that we can have effect modification on the risk difference scale ("statistical interaction") even when no synergism (or antagonism) is present. This will occur whenever  $(a_{12} - a_{012}) \neq 0$  i.e. when  $P(A_1 A_2) \neq P(A_0 A_1 A_2)$  or equivalently  $P(A_0 = 1|A_1 = 1, A_2 = 1) < 1$ .

Numerical Example 1 also sheds light on the conditions under which a multiplicative survival model can be used to test for synergism. The multiplicative survival model is said to hold when  $P(D = 0|E_1 = 1, E_2 = 1)P(D = 0|E_1 = 0, E_2 = 0) = P(D = 0|E_1 = 1, E_2 = 0)P(D = 0|E_1 = 0, E_2 = 1)$ . In Example 1, the probabilities of survival are:  $P(D = 0|E_1 = 0, E_2 = 0) = 1 - a_0$ ;  $P(D = 0|E_1 = 0, E_2 = 1) = 1 - a_0 - a_1 + a_{01}$ ;  $P(D = 0|E_1 = 0, E_2 = 1) = 1 - a_0 - a_2 + a_{02}$ ;  $P(D = 0|E_1 = 1, E_2 = 1) = 1 - a_0 - a_1 - a_2 + a_{01} + a_{02} + a_{12} - a_{012}$  and thus:  $P(D = 0|E_1 = 1, E_2 = 1)P(D = 0|E_1 = 0, E_2 = 0) = (1 - a_0)(1 - a_0 - a_1 - a_2 + a_{01} + a_{02} + a_{12} - a_{012}) = 1 - a_0 - a_1 - a_2 + a_{01} + a_{02} + a_{12} - a_{012} - a_0(1 - a_0 - a_1 - a_2 + a_{01} + a_{02} + a_{12} - a_{012})$ ; but  $P(D = 0|E_1 = 1, E_2 = 0)P(D = 0|E_1 = 0, E_2 = 1) = (1 - a_0 - a_1 + a_{01})(1 - a_0 - a_2 + a_{02}) = 1 - a_0 - a_1 + a_{01} - a_0 - a_2 + a_{02} + a_0^2 + a_0 a_2 - a_0 a_{02} + a_0 a_1 + a_1 a_2 - a_1 a_{02} - a_0 a_{01} - a_2 a_{01} + a_{01} a_{02}$ . Thus,  $P(D = 0|E_1 = 1, E_2 = 1)P(D = 0|E_1 = 0, E_2 = 0) - P(D = 0|E_1 = 1, E_2 = 0)P(D = 0|E_1 = 0, E_2 = 1) = (a_{12} - a_1 a_2) - (a_{012} - a_1 a_{02}) - (a_0 a_{12} - a_2 a_{01}) + (a_0 a_{012} - a_{01} a_{02}) \neq 0$  which will generally be non-zero so the multiplicative survival model will fail to hold in this example. However, if  $A_0, A_1$  and  $A_2$  were independently distributed then the above expression is zero and the multiplicative survival model holds. Somewhat more generally, if  $A_1$  and  $A_2$  were independent of one another and also either  $A_1$  or  $A_2$  were independent of  $A_0$  then the expression would again be zero and the multiplicative survival model would hold. Greenland and Poole proposed the multiplicative survival model as a means to assess the interdependence versus the independence of causal effects under the setting that the "effects of exposures are probabilistically independent of any background causes, as well as of one another's effect."<sup>6</sup> Example 1 underscores the necessity for the background causes to also be independent of one another when using the multiplicative survival model to detect the presence of synergism. More precisely, we have shown that if  $E_1$  and  $E_2$  have a positive monotonic effect on  $D$  and if  $A_1$  and  $A_2$  are independent of one another and either  $A_1$  or  $A_2$  is independent of  $A_0$  then the multiplicative survival model will hold when there is no synergism between  $E_1$  and  $E_2$ . Therefore, if, under these assumptions, the multiplicative survival model does not hold then one could conclude that synergism was present between  $E_1$  and  $E_2$ . Consideration of the use of the multiplicative survival model to test for interactions regarding biologic mechanisms is also given elsewhere.<sup>12,16</sup>

Numerical Example 2. We show that synergism may be present without effect modification of the risk difference. Suppose that  $D, E_1$  and  $E_2$  are binary, that  $E_1$  and  $E_2$  are independent and that  $D = A_0 \vee A_1 E_1 \vee A_2 E_2 \vee A_3 E_1 E_2$ . Then  $E_1$  and  $E_2$  have a positive monotonic effect on  $D$  and  $E_1$  and  $E_2$  do exhibit synergism. Suppose further

that the causal effects of  $E_1$  and  $E_2$  on  $D$  are unconfounded. Let  $P(A_0) = a_0, P(A_1) = a_1, P(A_2) = a_2, P(A_3) = a_3, P(A_0A_1) = a_{01}, P(A_0A_2) = a_{02}, \dots, P(A_0A_1A_2A_3) = a_{0123}$ . We then have  $P(D = 1|E_1 = 0, E_2 = 0) = P(A_0) = a_0$ ;  $P(D = 1|E_1 = 1, E_2 = 0) = P(A_0 \vee A_1) = a_0 + a_1 - a_{01}$ ;  $P(D = 1|E_1 = 0, E_2 = 1) = P(A_0 \vee A_2) = a_0 + a_2 - a_{02}$ ; and  $P(D = 1|E_1 = 1, E_2 = 1) = P(A_0 \vee A_1 \vee A_2) = (a_0 + a_1 + a_2 + a_3) - (a_{01} + a_{02} + a_{03} + a_{12} + a_{13} + a_{23}) + (a_{012} + a_{013} + a_{023} + a_{123}) - a_{0123}$ . Thus  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) - P(D = 1|E_1 = 1, E_2 = 0) + P(D = 1|E_1 = 0, E_2 = 0) = (a_{012} - a_{12}) + a_3 - (a_{03} + a_{13} + a_{23}) + (a_{013} + a_{023} + a_{123}) - a_{0123}$ . Suppose now that with probability 0.5,  $A_0 = 0, A_1 = 0, A_2 = 0, A_3 = 1$  and with probability 0.5,  $A_0 = 0, A_1 = 1, A_2 = 1, A_3 = 0$  so that  $a_3 = 0.5$  and  $a_{12} = 0.5$  and  $a_{012} = a_{03} = a_{13} = a_{23} = a_{013} = a_{023} = a_{123} = a_{0123} = 0$  then  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) - P(D = 1|E_1 = 1, E_2 = 0) + P(D = 1|E_1 = 0, E_2 = 0) = a_3 - a_{12} = 0.5 - 0.5 = 0$  and so although synergism is present the inequality  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) > P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0)$  fails to hold. The example demonstrates that although the inequality is a sufficient condition for synergism under the setting of monotonic effects, it is not necessary. It is also interesting to note that in this example  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) - P(D = 1|E_1 = 1, E_2 = 0) + P(D = 1|E_1 = 0, E_2 = 0) = \{a_3 - (a_{03} + a_{13} + a_{23}) + (a_{013} + a_{023} + a_{123}) - a_{0123}\} - (a_{12} - a_{012})$  and this final expression can be rewritten as  $P(A_3\bar{A}_0\bar{A}_1\bar{A}_2) - P(A_1A_2\bar{A}_0)$  suggesting that the more likely that  $A_3$  occurs when  $A_0, A_1, A_2$  are absent, the more power the test implied by Theorem 2 will have to detect the synergism; on the other hand the more likely that  $A_1$  and  $A_2$  occur together when  $A_0$  is absent, the less power the test implied by Theorem 2 will have to detect the synergism.

The contrast between Examples 1 and 2 is interesting. Example 1 demonstrated that effect modification could be present without synergism. In Example 1, effect modification on the risk difference scale would be present whenever  $P(A_1A_2) \neq P(A_0A_1A_2)$  suggesting that, in general, effect modification on the risk difference scale may be present without synergism if the various background causes  $A_0, A_1$  and  $A_2$  can occur simultaneously i.e. when multiple causal mechanisms may be simultaneously operative. It is, of course, also possible to have effect modification that is attributable solely to synergism rather than to the background causes. Example 2 considered the general case of synergism between  $E_1$  and  $E_2$  under the setting of monotonic effects. The expression for  $\{P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1)\} - \{P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0)\}$  could be rewritten as  $(a_{012} - a_{12}) + (a_3 - a_{03} - a_{13} - a_{23} + a_{013} + a_{023} + a_{123} - a_{0123})$ . For no effect modification on the risk difference scale to be present in Example 2 the sum of these two terms would have to be zero. Note that each part of the second term involves the subscript 3. The second term can thus be seen as the synergistic component; it will be zero when  $A_3 = 0$ . We saw in Example 1 that the first term being zero,  $(a_{012} - a_{12}) = 0$ , was the condition for no effect modification in the case of  $A_3 = 0$ . Suppose that  $(a_{012} - a_{12}) = 0$  but  $A_3 \neq 0$  and  $(a_3 - a_{03} - a_{13} - a_{23} + a_{013} + a_{023} + a_{123} - a_{0123}) \neq 0$  then the effect modification in Example 2 would be attributable solely to synergism (i.e. no effect modification would be present if  $A_3 = 0$ ). Thus in Example 1, the effect modification was wholly attributable to the possibility of the background causes  $A_0, A_1$  and  $A_2$  occurring simultaneously and in Example 2, if  $(a_{012} - a_{12}) = 0$ , the effect modification would be wholly attributable to the

presence of synergism. In general, effect modification may arise either due to background causes or due to the presence of synergism or due to both.

Numerical Example 3. We show that without monotonic effects, one may have "super-additive" effect modification of the risk difference without definite interdependence or synergism. Suppose that  $D$ ,  $E_1$  and  $E_2$  are binary, that  $E_1$  and  $E_2$  are independent and that  $D = A_1E_1 \vee A_2\overline{E_1} \vee A_3\overline{E_2}$ . Then  $E_1$  and  $E_2$  do not exhibit definite interdependence. Suppose further that the causal effects of  $E_1$  and  $E_2$  on  $D$  are unconfounded. Finally, suppose that with probability 0.3,  $A_1 = 1, A_2 = 0, A_3 = 1$ ; with probability 0.3,  $A_1 = 1, A_2 = 0, A_3 = 0$ ; and with probability 0.4,  $A_1 = 0, A_2 = 1, A_3 = 0$  so that  $a_1 = 0.6$ ,  $a_2 = 0.4$ ,  $a_3 = 0.3$ ,  $a_{13} = 0.3$  and  $a_{23} = 0$ . We then have  $P(D = 1|E_1 = 0, E_2 = 0) = P(A_2 \vee A_3) = a_2 + a_3 - a_{23}$ ;  $P(D = 1|E_1 = 1, E_2 = 0) = P(A_1 \vee A_3) = a_1 + a_3 - a_{13}$ ;  $P(D = 1|E_1 = 0, E_2 = 1) = P(A_2) = a_2$ ; and  $P(D = 1|E_1 = 1, E_2 = 1) = P(A_1) = a_1$ . Conditional on  $E_2 = 0$ , the risk difference for  $E_1$  is given by:  $P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0) = a_1 + a_3 - a_{13} - (a_2 + a_3 - a_{23}) = a_1 - a_2 - a_{13} + a_{23} = 0.6 - 0.4 - 0.3 = -0.1$ . Conditional on  $E_2 = 1$ , the risk difference for  $E_1$  is given by:  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) = a_1 - a_2 = 0.6 - 0.4 = 0.2$ . In this example,  $P(D = 1|E_1 = 1, E_2 = 1) - P(D = 1|E_1 = 0, E_2 = 1) > P(D = 1|E_1 = 1, E_2 = 0) - P(D = 1|E_1 = 0, E_2 = 0)$  but no synergism was present. We see also from this example that we can have qualitative effect modification even when no synergism is present.

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