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Analytical Implications of Epidemiological Concepts of Interaction

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In contrast to definitions based on statistical or biological concepts, Rothman has adopted an unambiguous epidemiological definition of interaction in which two factors are not 'independent' if they are component causes in the same sufficient cause. This leads to the adoption of additivity of incidence rates as the state of 'no interaction'. However, there are other considerations which generally favour the use of multiplicative models. This implies an apparent dilemma as to how an analysis can be conducted which combines the advantages of ratio measures of effect with the assessment of independence in terms of a departure from additivity. These apparently contradictory goals can be reconciled through the analysis of separate and joint effects. This approach is discussed with reference to studies of asbestos exposure, cigarette smoking and lung cancer.

In the late 1970s, readers of epidemiological journals witnessed a lively discussion on concepts of interaction. In 1980 Rothman *et al.*[1] proposed that the controversy could be laid to rest by distinguishing four broad contexts in which interaction could be evaluated: statistical, biological, public health, and individual decision-making. Rothman[2] has more recently embedded the concept of epidemiological interaction into his theory of 'causal constellations'.[3] The intention of this paper is not to resurrect the previous debate, but rather to explore the analytical implications of these concepts. The resulting analytical strategy is not new, but the discussion is intended to clarify the reasons for its use, and the potential pitfalls of statistically-based strategies which are also in common use.

EFFECT MODIFICATION AND STATISTICAL INTERACTION

The analytical issues will be illustrated with data from a study by Selikoff *et al.*[4] of lung cancer death rates per 100 000 person-years at risk in relation to exposure to cigarette smoke and asbestos:[5]

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		Smoking	
		Yes	No
Asbestos	Yes	935.8	500.5
	No	199.5	28.6

The rate difference due to asbestos exposure is 471.9 per 100 000 person-years in non-smokers and 736.3 per 100 000 person-years in smokers. Thus, smoking increases the effect of asbestos exposure on lung cancer mortality (as measured by the rate difference). On the other hand, the rate ratio due to asbestos exposure is lower in smokers (asbestos rate ratio = 4.7) than in non-smokers (asbestos rate ratio = 17.5). Thus, both the rate difference and the rate ratio are subject to 'effect modification' in that the effect estimate depends on the presence or absence (or more generally, the level) of another factor.[6] The term 'statistical interaction' denotes essentially the same phenomenon but without the causal connotation.

Several authors[7,8] have demonstrated the dependence of statistical interaction on the underlying statistical measure of effect, and have therefore argued that the assessment of interaction is 'model-dependent'. It is not clear why such a statistical phenomenon should be of inherent interest to epidemiologists. Neverthe-

less, some authors[9] have developed modelling strategies in which the first step of an analysis involves testing for statistical interaction. In the most extreme application this involves including all possible two-factor (and even three-factor) interactions in a preliminary model and retaining in subsequent analyses all variables (and related lower-order terms) which are statistically significant in the preliminary model. This approach often results in complex models with numerous interaction terms, which may lead to problems of convergence or difficulties in interpretation. This problem has led to the development of generalized families of models which include the additive and multiplicative models as special cases.[10-12] These models may avoid the need for interaction terms, but introduce other complexities in turn, and the resulting loss of epidemiological interpretability may often outweigh their statistical advantages.[13]

EPIDEMIOLOGICAL AND BIOLOGICAL CONCEPTS OF INDEPENDENCE OF EFFECTS

In contrast to these statistically-based approaches, Rothman[2] adopts an unambiguous epidemiological definition of interaction in which two factors are not 'independent' if they are component causes in the same sufficient cause. This concept of independence of effects leads to the adoption of additivity of incidence rates as the state of 'no interaction'. One apparent exception should be noted.[14] If two factors (A and B) belong to different sufficient causes, but a third factor (C) belongs to both sufficient causes, then A and B are competing for a single pool of susceptible individuals (those who have C). Consequently the joint effect of A and B will be less than additive (Miettinen[15] reaches a similar conclusion based on a model of individual outcomes). However, this phenomenon can be incorporated directly into the causal constellation model by clarifying a previous ambiguity in the description of antagonism in the model's terms. Specifically, the *absence* of B can be included in the causal constellation involving A, and vice versa. Then, two factors would not be 'independent' if the *presence or absence* of the factors (or particular levels of both factors) were component causes in the same sufficient cause.[16]

It should be stressed that this epidemiological concept of independence of effects is distinct from biological concepts of independence. For example, Siemiatycki and Thomas give a definition in which two factors are considered to be biologically independent 'if the qualitative nature of the mechanism of action of each is not affected by the presence or absence of the other'.[17] However, this concept does not lead to an unambiguous definition of independence of effects,[17] and thus does not produce clear analytical implications. Rothman's concept of independence is at a more fundamental conceptual level in which a particular biological model, rather than being accepted as the 'baseline', is itself evaluated in terms of the co-participation of factors in a sufficient cause. For example, two factors which act at different stages of a multistage process are not independent since they are joint components of at least one sufficient cause. This occurs irrespective of whether they affect each other's qualitative mechanism of action (the ambiguity in Siemiatycki and Thomas' formulation stems from the ambiguity of this concept).

ADDITIVE AND MULTIPLICATIVE MODELS

Rothman's approach is attractive because it is based on epidemiological concepts which have a clear biological interpretation, and because it leads to an unambiguous definition of independence of effects which is identical to that obtained through public health considerations.[1] However, the analytical implications of these concepts are not straightforward, since assessing independence of effects is usually only one of the analytical goals of an epidemiological study. There are several other considerations which often favour the use of multiplicative models.

First, multiplicative models have convenient statistical properties. Estimation in non-multiplicative models may have problems of convergence, and inference based on the asymptotic standard errors may be flawed unless the study size is very large.[18]

Second, multiplicative models facilitate the assessment of the extent of unknown confounding or bias.[19]

Third, if it is desired to keep statistical interaction (effect modification) to a minimum, then a multiplicative model may be more appropriate. It is not uncommon for risk factors to have approximately multiplicative effects.[20] This presumably occurs because they are a part of common causal processes, although other sufficient causes usually also operate, and exact multiplicativity may not occur. Nevertheless, in this situation there may be less masking of heterogeneity in calculating an overall rate ratio than in calculating an overall rate difference (there are also many instances of non-multiplicative departures from additivity, however).[4,20]

JOINT EFFECTS

These considerations imply an apparent dilemma. How can an analysis be conducted which combines the advantages of ratio measures of effect with the assessment of independence in terms of a departure from additivity? These apparently contradictory goals can

be reconciled in analyses which concentrate on the estimation of *separate* and *joint effects*.

Thus, when studying asbestos, smoking and lung cancer, relative risks might be presented for smoking (in non-asbestos workers), asbestos exposure (in non-smokers) and exposure to both factors, relative to people exposed to neither factor. These relative risks would be adjusted for all other factors (eg, age) which are potential confounders, but not of immediate interest as effect modifiers. The relevant table can be derived from *any* form of model, including the statistically convenient multiplicative models, by including an appropriate interaction term.

The estimation of separate and joint effects may be difficult when the factors of interest are closely correlated. However, when it is feasible, this approach combines the best features of multiplicative models and additive independence assessment, but also permits readers with other concepts of independence to draw their own conclusions. It can be illustrated with the data presented above on asbestos exposure, cigarette smoking, and lung cancer. In this example, the relative risk estimates (adjusted for age and calendar period) are:

		Smoking	
		Yes	No
Asbestos	Yes	32.7	17.5
	No	7.0	1.0

Thus, the joint effect of asbestos and smoking is more than additive (the joint effect is 32.7 times, whereas it would be $1+(7.0-1)+(17.5-1) = 23.5$ if it were additive). This is consistent with the hypothesis that asbestos and smoking are joint components in at least one sufficient cause (it might be argued that non-additivity refutes the hypothesis that asbestos and smoking never biologically interact, but such 'refutation' depends on the untestable assumption that there is no unknown confounding or bias). If their joint effect were the sum of their independent effects, then this would have supported the hypothesis that they are not joint components of a sufficient cause or competing for a common pool of susceptibles. However, the interpretation is not unambiguous, since additivity could arise if two factors were components of the same sufficient cause, but influenced each other's biological mechanism of action (thus, even in ideal circumstances, additivity does not refute the hypothesis that asbestos and smoking interact).

If it is provisionally accepted that smoking and asbestos do belong to at least one common causal constellation for lung cancer, then attention shifts to elaborating the effect with deductive models. For example, Doll and Peto[21] have suggested that smoking acts at both an early stage (probably the second) and the penultimate (fifth) stage of a six-stage carcinogenic process. Asbestos appears to act at one of the later stages, probably the fourth or fifth.[22,23] If asbestos acted at the *same* late stage as smoking, then it could be expected that its effect would add onto the late stage effect of smoking, and multiply the early stage effect of smoking. The resulting joint effect would be intermediate between additive and multiplicative. This pattern has been observed in several studies[4] (there are, of course, other models which predict the same result).[20]

GENERAL IMPLICATIONS

These considerations have implications for generalized modelling strategies. Such strategies may often be of limited value, since there would appear to be no need for statistical decision rules if the reasons for studying a particular constellation of risk factors are clear. If the reasons are not clear then such rules may not help, and may actually discourage the investigator from thinking more deeply about the analysis. Nevertheless, it is interesting to speculate, in very general terms, on the different analytical strategies which arise from the above epidemiological concepts of interaction, in contrast to those which arise from statistical concepts.

A key implication is that there is no logical necessity for the assessment of interaction to occur as the first step in an analysis. In fact, there are at least three reasons why it is preferable to evaluate confounding before considering interaction.

First, the initial aim of most analyses is to determine if there is any overall effect of exposure. It is necessary to control confounding to do this, but there is no necessity to evaluate interaction.[24] It is true that harmful effects in one stratum and protective effects in another stratum may yield an overall null effect. However, this phenomenon is presumably rare, and a routine search may yield a high percentage of false positives (obviously, if there was a relevant *a priori* hypothesis then it would be appropriate to calculate stratum-specific effect estimates irrespective of the value of the summary effect estimate).

A second reason for evaluating confounding before considering interaction is that the inclusion of interaction terms involving the main exposure complicates confounder assessment, since changes in the interaction coefficients must be examined as well as changes in the main exposure coefficients.

Third, even if subsequent analyses concentrate on specific subgroups, it may be preferable to evaluate confounding in the whole data set, since this provides

the greatest precision. If a factor is a confounder overall, then it is a risk factor, and is also associated with exposure. Thus it is necessarily a confounder in some specific subgroups, and there may be little loss of precision from control in any subgroups in which it is not a confounder (although this cannot be guaranteed). Hence, it may be preferable to evaluate confounding first, and then adjust for the same confounders in each subgroup analysis.

Two qualifications should be noted. First, confounding may be evaluated purely on *a priori* considerations, but this situation applies equally to the various modelling strategies. Second, it may be desirable to include interaction terms involving only covariates rather than the main exposure.[2] However, this is done for confounder control rather than interaction assessment.

If an excess risk is found (and assumed to be causal) then attention shifts to elaborating the nature of the effect. This naturally comes at the end of the formal presentation of the findings. Typically, the last few tables of a manuscript might examine the joint effects of the main exposure with other factors of interest, and the discussion might relate these findings to current aetiological knowledge. As noted above, it is usually only useful to evaluate joint effects for which there is an *a priori* reason for interest. However, when this evaluation occurs as the last stage of an analysis, the routine evaluation (screening) of a large number of joint effects is relatively straightforward, since this merely increases the number of tables, but does not unnecessarily complicate other aspects of the analysis.

A related question is whether statistical tests for interaction should be performed. This issue mirrors previous debates regarding testing for main effects. As has been argued for main effects,[2] it is the strength of an interaction that is important (from an epidemiological perspective) rather than its statistical significance. Furthermore, in a multiplicative model, the standard test for interaction is inappropriate since it evaluates departures from multiplicativity, whereas it is departures from additivity that are of interest. Even an appropriately formulated test is of limited value since such tests usually have low power[25] and few genuine statistical interactions will be statistically significant. On the other hand, it *is* useful to present confidence intervals for the estimates of separate and joint effects. This information can then be used by other researchers when reviewing the consistency of published studies.

CONCLUSIONS

There has previously been much debate on concepts of interaction. However, there has been little debate on the analytical implications of these concepts, and analytical strategies have generally been based on statistical criteria. Ultimately, all cases of disease arise from the effects of more than just one factor. Without interaction, there would be no disease. Every effect estimate thus neglects numerous unknown or unmeasured modifying factors. The problem of interaction must therefore be approached in a manner which facilitates the understanding of the nature of the causal effect; statistical considerations should serve rather than determine our objectives.

Conventional statistical analysis strategies are based on the principle that it is not appropriate to calculate an overall effect estimate if interaction is present. However, this principle is commonly ignored if the difference in stratum-specific effect estimates is not too great. In fact standardized rate ratios[26] have been developed for precisely this situation, and will consistently estimate meaningful epidemiological parameters even under heterogeneity.[27] Nevertheless, some authors have proposed modelling strategies in which the first step in the analysis involves testing for statistical interaction. A related approach has been the development of generalized families of models which include the additive and multiplicative models as special cases.

In this paper an alternative general strategy has been proposed, based on epidemiological considerations. The key difference is that interaction is assessed (rather than tested) in terms of a departure from additivity in order to elaborate an observed effect, rather than being tested for departure from an arbitrary effect measure as an essential initial analytical step. This procedure can be achieved within the confines of statistically convenient multiplicative models through the analysis of separate and joint effects.

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