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ASSESSMENT OF ADDITIVE AND MULTIPLICATIVE INTERACTION USING RECONSTRUCTED DATA: EVIDENCE FROM HYPERTENSION RISK FACTORS IN EDO STATE, NIGERIA

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ABSTRACT

Interaction is a measure of the joint effect of two factors on an outcome compared to their individual effects. Factorial experiment provides a good background for the analysis of interaction among two or more factors. In epidemiology, the joint effect of two or more risk factors is mostly assessed using additive and multiplicative interaction scales.

This study examines additive and multiplicative interaction between tobacco and alcohol and their effect on development of hypertension using reconstructed contingency data. In order to assess interaction, we reconstructed a three-way contingency data by algebraic procedure from marginal totals obtained from a study of oil palm workers in Edo State, Nigeria.

The result showed evidence of positive interaction on both additive and multiplicative scales justifying the presence of interaction in the data and the validity of the reconstructed three-way contingency data. We concluded that from the additive scale about 9.4% of the hypertensive cases can be attributed to interaction, while on the multiplicative scale about 52% of the jointly exposed individuals are more likely to develop hypertension.

1. INTRODUCTION

Interaction plays a central role both in statistical modelling and epidemiological studies. It entails a situation where the joint effect of two factors differs from the expected individual effects of the factors. The work of [1] and later [2] made outstanding effort to relate the concept of interaction in factorial experiment and interaction in epidemiology, also known as synergism. Earlier, [3] worked on measure of interaction which [4] later referred to as Interaction Contrast of Disease Ratio (I.C.D.R). Subsequently, [5] developed these ideas to include interactions in multi-factor settings. Meanwhile [6] and [7] had noted that there is a difference between statistical interaction and biological interaction.

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More recently, [8] unified interaction concepts across epidemiology and statistical models. Their work documented many forms of synergism and scenarios where they are applied. In [9], deviations from additive interaction among multiple binary exposures were examined. They used the relative excess risk due to interaction (RERI) as a measure of additive interaction. Their approach gave interpretation for deviations from additivity resulting from three or more risk factors and provides ways of communicating the result in public health by attributing any excess relative risk to combinations of these factors.

The work of [10] stated that if the relative magnitude of effects across subgroups is of interest then there exists an "interaction continuum" that characterizes the nature of these relations. He explained that if the main effects of two factors are positive then the continuum will depend on the relative value of the probability of the outcome in the doubly exposed group. High probabilities of the outcome in the doubly exposed group, entails interaction may be positive-multiplicative positive-additive, which is the strongest form of positive interaction on the "interaction continuum". However, as the probability of the outcome in the doubly exposed group declines, the form of interaction descends through ranks. In [11] they proposed the use of "Relative Risk Reduction due to Interaction" (RRRI) for accessing additive interaction between risk factors known to prevent the event's occurrence, such as medical interventions and drugs. A description of how the Relative Excess Risk due to Interaction (RERI) and other measures of additive interaction or effect modification can be validly estimated was given in [12]. They explained why direct pooling of study-level RERI estimates may lead to invalid results. They illustrated the procedure using a data investigating the interaction between depression and smoking.

In this work we examined both additive and multiplicative interaction from a two-level factorial design and compared the two concepts using a two-way contingency data on the influence of tobacco and alcohol use on development of hypertension among workers of an oil palm company in Edo State, Nigeria as in [13]. Since interaction can only be assessed when data on joint exposure is available, we reconstructed a three-way contingency data from the marginal totals given in the original data and compared how the two scales (additive and multiplicative) of interaction can best describe the joint effect of two risk factors in epidemiological studies.

2.0 ADDITIVE INTERACTION MODEL

Consider a two-level factorial design, that is, an experiment having several factors each at two levels. The design is denoted as 2^n, where two is the number of levels and n is the number of factors. For instance, when n = 2, then we are looking at a 2^2 factorial experiment with factors say P and Q each at two levels. Assuming the levels of P are P_0 *and* P_1 and the levels of Q are Q_0 *and* Q_1, then the treatment combinations may be $P_0Q_0, P_0Q_1, P_1Q_0,$ *and* P_1Q_1. The contrast $(P_1Q_0 - P_0Q_0)$ is the main effect of P with respect to the reference category. Similarly, the contrast $(P_0Q_1 - P_0Q_0)$ is the main effect of Q with respect to the reference category. In addition the contrast $(P_1Q_1 - P_0Q_0)$ is the interaction effect of both P and Q with respect to the reference category. Note here the if the two factors P and Q are independent then there is no interactions and,

$$P_1Q_0 - P_0Q_0 = P_1Q_1 - P_0Q_1 \quad (1)$$

Also,

$$P_0Q_1 - P_0Q_0 = P_1Q_1 - P_1Q_0 \quad (2)$$

Equations (1) and (2) entail that at different levels of Q and P the effects of P and Q are respectively the same.
The measure of interaction involves determination of the extent to which the effect of both factors together differs from effects of the individual main effects (Rothman, 1986; Szklo and Nieto, 2007).
This is given by,

$$(P_1Q_1 - P_0Q_0) - [(P_1Q_0 - P_0Q_0) + (P_0Q_1 - P_0Q_0)] \quad (3)$$

or

$$P_1Q_1 - P_1Q_0 - P_0Q_1 + P_0Q_0 \quad (4)$$

Equation (4) above is the measure of interaction in the additive scale. If

$$P_1Q_1 - P_1Q_0 - P_0Q_1 + P_0Q_0 > 0 \quad (5)$$

we have a positive additive interaction and a negative additive interaction when

$$P_1Q_1 - P_1Q_0 - P_0Q_1 + P_0Q_0 < 0 \quad (6)$$

If $P_1Q_1 - P_1Q_0 - P_0Q_1 + P_0Q_0 = 0$ (7)

it clearly indicates the absence of interaction among the factors considered.

For an epidemiological study with a binary outcome (disease; D = 1 (yes) or D = 0 (no)) and two dichotomous exposures or risk factors $\left(p(p_0, p_1)\ and\ q(q_0, q_1)\right)$, interaction is assessed by the probability of the outcome. Let $r_{pq} = Prob(D = 1|p = p_i, q = q_i), i = 0,1$; be the probability of the outcome when p is at p_i and q is at q_i [8]. As in equation (4) above the measure of interaction is assessed as,

$$r_{11} - r_{10} - r_{01} + r_{00} \quad (8)$$

Consider an illustrative example using 2x2 contingency data on Prevalence and Risk Factors of Hypertension among Workers of an Oil Palm Company in Edo State, Nigeria [13]. The data is originally on the marginal effects of tobacco and alcohol use on development of hypertension but did not provide the joint effect of both exposures, which is required for assessment of interaction. In order to assess interaction, we require a 2x2x2 contingency data. Here a three-way contingency table will be reconstructed using the marginal totals reported.

2.1 Reconstruction of Joint Exposure Data

The oirginal data is,

Table 1: Marginal data on hypertensive status and influence of tobacco and alcohol use

Variable	Hypertensive Status	
	Yes	No
Current Tobacco Use		
Yes	5	11
No	60	278
Alcohol Use		
Yes	28	144
No	37	145

From the data above we deduced that the total number hypertensive status (Yes) for both tobacco use and alcohol use is the same (n=65), similarly the total number hypertensive status (No) for both tobacco use and alcohol use is also the same (n=289). As such the data on tobacco and alcohol use were extracted from the same set of subjects, justifying the possibility of interacting or joint exposures.

Let's denote t_0, t_1, a_0 and a_1 as a subject who is a non-user of tobacco, a user of tobacco, a non-user of alcohol and a user of alcohol respectively.

For hypertension (Yes), where n = 65, we state the following constraints.

$x_1: (t_0, a_0)$; indicating subjects who are non-users of both tobacco and alcohol

$x_2: (t_0, a_1)$; indicating subjects who are non-users of tobacco but users of alcohol

$x_3: (t_1, a_0)$; indicating subjects who are users of tobacco but non-users of alcohol

$x_4: (t_1, a_1)$; indicating subjects who are users of both tobacco and alcohol

$$x_1 + x_2 + x_3 + x_4 = 65 \; , x_i \geq 0; i = 1,2,3,4. \quad (9)$$

Then,
for tobacco use and hypertension yes,

$$x_3 + x_4 = 5 \quad (10)$$

for non-tobacco use and hypertension yes,

$$x_1 + x_2 = 60 \quad (11)$$

for alcohol use and hypertension yes,

$$x_2 + x_4 = 28 \quad (12)$$

for non-alcohol use and hypertension yes,

$$x_1 + x_3 = 37 \quad (13)$$

From equations (10) to (13) we have a system of four linear equations in four unknowns;

$$\left.\begin{aligned} x_3 + x_4 &= 5 \\ x_1 + x_2 &= 60 \\ x_2 + x_4 &= 28 \\ x_1 + x_3 &= 37 \end{aligned}\right\} \quad (14)$$

Evaluating, we let $x_4 = u; u \geq 0$, then from equation (10),

$$x_3 = 5 - u \quad (15)$$

From equation (12),

$$x_2 = 28 - u \quad (16)$$

From equations (12) and (15),

$$x_1 = 32 + u \quad (17)$$

Since $x_i \geq 0$, it implies that from equations (15) and (16),

$0 \leq u \leq 5$ and $0 \leq u \leq 28$, respectively. The two inequalities restrict u within the interval $0 \leq u \leq 5$.

Hence, choosing u arbitrary from the interval, say $u = 3$, we have the solution of $x_i's$ as

$x_1 = 35, x_2 = 25, x_3 = 2$ and $x_4 = 3$, satisfying the constraint in equation (9).

Hence we obtain a three-way contingency table suitable for interaction analysis as,

Table 2: Reconstructed data on hypertensive status (yes) and influence of tobacco and alcohol use

	No Tobacco	Tobacco
No Alcohol	35	2
Alcohol	25	3

Epidemiological interaction is computed from the risk of experiencing the outcome of interest given the presence or absence of the exposures or risk factors. So using x_i as defined we compute the risk of hypertension among the four groups as,

$$r_{pq} = \frac{x_i}{x_i + y_i}, \ p, q = 0,1 \quad (18)$$

where y_i corresponds to the number of subjects who are exposed in the same class but do not have the outcome of interest, that is hypertensive (no). To obtain $y_i's$, repeat the steps in reconstructing the original data, but now using hypertensive status (no). That is,

For hypertension (No), where n = 289, we state the following constraints.

$y_1: (t_0, a_0)$; indicating subjects who are non-users of both tobacco and alcohol

$y_2: (t_0, a_1)$; indicating subjects who are non-users of tobacco but users of alcohol

$y_3: (t_1, a_0)$; indicating subjects who are users of tobacco but non-users of alcohol

$y_4: (t_1, a_1)$; indicating subjects who are users of both tobacco and alcohol

$$y_1 + y_2 + y_3 + y_4 = 289 \ , y_i \geq 0; i = 1,2,3,4. \quad (19)$$

Then,

for tobacco use and hypertension (no),

$$y_3 + y_4 = 11 \quad (20)$$

for non-tobacco use and hypertension (no),

$$y_1 + y_2 = 278 \quad (21)$$

for alcohol use and hypertension (no),

$$y_2 + y_4 = 144 \quad (22)$$

for non-alcohol use and hypertension (no),

$$y_1 + y_3 = 145 \quad (23)$$

Let $y_4 = v$ and solving the resulting system of linear equations, we have the restriction on v as $0 \leq v \leq 11$. Choosing, $v = 6$, arbitrary we have, $y_1 = 140, y_2 = 138, y_3 = 5,$ and $y_4 = 6$

Table 3: Reconstructed data on hypertensive status (no) and influence of tobacco and alcohol use

	No Tobacco	Tobacco
No Alcohol	140	5
Alcohol	138	6

Then using the expression in equation (18) and values in Tables 2 and 3,

$r_{00} = \frac{35}{35+140} = 0.2$, $r_{01} = \frac{25}{25+138} = 0.1534$, $r_{10} = \frac{2}{2+5} = 0.2857$, $r_{11} = \frac{3}{3+6} = 0.3333.$

Hence, the risks of hypertension in the four groups are given below in Table 4.

Table 4: Risk of Hypertension by Tobacco and Alcohol use

	No Tobacco	Tobacco
No Alcohol	0.2000	0.2857
Alcohol	0.1534	0.3333

Using the expression in equation (8), we have the measure of additive interaction as,
$0.3333 - 0.2857 - 0.1534 + 0.2 = 0.0942$

Since we have a value greater than zero, there is evidence of positive interaction suggesting that about 9.4% of the hypertension cases among individuals who are jointly exposed to tobacco and alcohol use are attributable to interaction.

3.0 MULTIPLICATIVE INTERACTION MODEL

Interaction in epidemiology can be assessed through additive or multiplicative scales. While the additive scale uses the risk differences to determine the magnitude and direction of interaction, the multiplicative scale on the other hand uses the risk ratios or odd ratios. These ratios are computed using the risk of occurrence of the disease given the presence or absence of an exposure(s). Here we present the expressions for computing risk ratio and odd ratio for a given outcome and apply it to the hypertension data in Table 4, then compare the results with that of the additive interaction.

3.1 Assessing Multiplicative Interaction using Risk Ratios

Multiplicative interaction using risk ratios entails computing the ratio of the risk ratio of the outcome given both exposures (RR_{11}), to the product of the risk ratios of the outcome given individual exposures (RR_{10}) and (RR_{01}) . That is, for

$$RR_{11} = \frac{r_{11}}{r_{00}}$$
$$RR_{10} = \frac{r_{10}}{r_{00}}$$
$$RR_{01} = \frac{r_{01}}{r_{00}}$$

The multiplicative interaction could be measured as:

$$\frac{R_{11}}{R_{10}R_{01}} = \frac{r_{11}r_{00}}{r_{10}r_{01}}$$

Unlike the additive scale, if $\frac{R_{11}}{R_{10}R_{01}} > 1$, the multiplicative interaction is positive and negative if $\frac{R_{11}}{R_{10}R_{01}} < 1$. In other hand, if $\frac{R_{11}}{R_{10}R_{01}} = 1$, then the effect on the outcome of the presence of both exposures is the same as the product of the effects of individual exposures, hence there is no interaction.

For the hypertension data in Table 4, the multiplicative interaction is given by:

$$RR_{11} = \frac{0.3333}{0.2000} = 1.6665$$
$$RR_{10} = \frac{0.2857}{0.2000} = 1.4285$$
$$RR_{01} = \frac{0.1534}{0.2000} = 0.7670$$

$$\frac{R_{11}}{R_{10}R_{01}} = \frac{1.6665}{(1.4285)(0.7670)} = 1.5210$$

Since the ratio is greater than one, there is evidence of positive interaction, suggesting that about 52% of the relative risk of hypertension among those individuals who are jointly exposed to tobacco and alcohol use are largely due to interaction.

3.2 Assessing Multiplicative Interaction using Odd Ratios

Here we compute the odd of an outcome occurring given the presence or absence of an exposure(s). Where OR_{11} is the odd of the outcome given both exposures, and RR_{10} and RR_{11} the odds of the outcome given individual exposures. A measure of multiplicative interaction on the odd ratio scale is the ratio of the odd of the outcome for both exposures to the product of the odds of the outcome for individual exposures. That is,

$$OR_{11} = \frac{r_{11}/(1 - r_{11})}{r_{00}/(1 - r_{00})}$$

$$OR_{10} = \frac{r_{10}/(1 - r_{10})}{r_{00}/(1 - r_{00})}$$

$$OR_{01} = \frac{r_{01}/(1 - r_{01})}{r_{00}/(1 - r_{00})}$$

The multiplicative interaction could be measured as:

$$\frac{OR_{11}}{OR_{10}OR_{01}} = \frac{r_{11}r_{00}(1 - r_{10})(1 - r_{01})}{r_{10}r_{01}(1 - r_{11})(1 - r_{00})}$$

Like in risk ratio if $\frac{OR_{11}}{OR_{10}OR_{01}} > 1$, the multiplicative interaction is positive and negative if $\frac{OR_{11}}{OR_{10}OR_{01}} < 1$. In other hand, if $\frac{OR_{11}}{OR_{10}OR_{01}} = 1$, then the effect on the outcome of the presence of both exposures is the same as the product of the effects of individual exposures, hence there is no interaction.

For the hypertension data in Table 4, the multiplicative interaction under the odd ratio scale is given by:

$$OR_{11} = 1.3888$$
$$OR_{10} = 1.2755$$
$$OR_{01} = 0.8117$$

$$\frac{OR_{11}}{OR_{10}OR_{01}} = \frac{1.3888}{(1.2755)(0.8117)} = 1.3414$$

Since the ratio is greater than one, there is evidence of positive interaction.

Observe that the multiplicative interaction in the old ratio scale is close to that of the risk ratio scale. In general, under the multiplicative interaction, the odd ratio and risk ratio are usually close to each, and connotes the same meaning and interpretation, especially for rare diseases.

4.0 COMPARISON OF ADDITIVE AND MULTIPLICATIVE INTERACTION

The data on hypertension used above gave positive interaction on both the additive and multiplicative scales; this is not usually the case. Depending on the risk of outcome, interactions could be positive on both scales, negative on both scales, positive in one and negative in the other or present (positive or negative) in one scale but absent in the other. This entails that interaction depends on the scale used and poses the question, "which among the two scales best represent interaction in epidemiological studies". Interaction studies have always advised that both scales should be reported as they are differently informative with respect to the study objectives; see [16], [17] and [18].

On the additive scale interaction is assessed in terms of excess attributable risk due to the effect of both exposures. It measures whether the joint effect of both exposures exceeds the sum of the individual effects of both exposures. This scale is important in epidemiology because it gives insight into biological interaction and provides evidence of the likely cause of a disease and possible direction of intervention. For instance, the positive interaction in the hypertension data indicates that a proportion (about 9.4%) of the disease among individuals exposed to both tobacco and alcohol is mainly due to interaction, which has direct importance in public health.

In contrast, interaction on the multiplicative scale evaluates whether the joint effect of two exposures exceeds the product of their individual effects using either the risk ratios or the odd ratios. This is a measure of the relative effects of both exposures and not the absolute difference as in additive interaction. The multiplicative interaction scale is widely used in modeling, like in logistic regression as in [8], where interaction is given by a product term between variables. Multiplicative interaction is usually easier to compute and used for statistical inference, which explains why most epidemiological journals reports interaction using the multiplicative scale rather than the additive scale [19]. Also, most available software packages are built to assess interaction on the multiplicative scale [8]. This popular use and acceptance of multiplicative interaction does not make it more valuable than additive interaction as does not necessarily reflect biological synergy, as absence of multiplicative interaction does imply absence of additive interaction.

In this study we determined both additive and multiplicative scales of interaction and both provided strong evidence that a proportion of the disease (hypertension) is due to the effect of both risk factors (tobacco and alcohol use). While the additive scale gave the proportion having hypertension due to interacting risk factors, the multiplicative scale showed that statistics supports the result. It is therefore advised that both scales should be reported for any epidemiological study assessing interaction.

DISCUSSION

This study assessed interaction between tobacco and alcohol use and its relation to hypertension using both additive and multiplication scales, based on a three-way contingency table reconstructed from a two-way marginal data. The study gave positive additive interaction of 0.0942 and positive multiplicative interaction of 1.5210. This reinforces the fact that the joint effect of tobacco and alcohol use on hypertension exceeds both the sum and product of their individual effects.

The additive interaction suggests that approximately 9.4% of the risk of hypertension among those exposed to both tobacco and alcohol use is due to interaction. This is an excessive risk above what it could have been if the effects of the two exposures were assessed individually. This is important for public health as it highlights the subgroup that bear greater burden of the disease and focus intervention on it. The multiplicative interaction on the other hand, gave an estimate of 1.5210 indicating that the combined effect of tobacco and alcohol use is approximately 52% higher than the expected product of the individual exposures. This shows that there is an effect modification and justifies the claim that the joint exposure substantially increases the risk of hypertension.

An important methodological aspect of this study is the reconstruction of the joint exposure data from the marginal two-way contingency table in the original study. Most epidemiological studies only report marginal associations between risk factors and the outcome, making it impossible to directly assess interaction when it truly exists. The reconstruction of a three-way contingency in this study gave a practical approach for measuring interaction between two exposures given an incomplete marginal data, provided that both exposures are from the same population.

CONCLUSION

In this study we demonstrated that tobacco and alcohol use have an interacting influence on the risk of hypertension. The presence of positive interaction in both the additive and multiplicative scale shows that the joint effect of these exposures is evidently higher than what is expected from only their individual effects. The additive interaction evaluated showed that the proportion of hypertension risk among the individuals who are doubly exposed is attributable to interaction. Meanwhile, the multiplicative interaction confirms that the joint exposure raises relative risk and supports the observed impact. These findings highlight the need to jointly target intervention on multiple exposures, rather than individually. Public health policies targeting reduction of hypertension should consider the combined effects of subject's lifestyle such as tobacco and alcohol use. This study also showed the usefulness of reconstructing joint exposure from marginal data to enable the assessment of interaction, when a complete data is unavailable. Finally, reporting both the additive and multiplicative interaction gives a better understanding of the etiology of the disease and should be part of any epidemiological study assessing interaction for multiple risk factors.

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