Nutritional status in chronic dialysis patients : associations with development of disease and survival

Mutsert, R. de

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The effect of joint exposures: Examining the presence of interaction

R. de Mutsert
K.H. Jager
C. Zoccali
F.W. Dekker

Kidney Int 2009, in press

ABSTRACT

Many clinical epidemiological studies investigate whether an exposure, or risk factor, is causally related to the development or progression of a disease or mortality. It might be of interest to study whether this relation is different in different types of patients. To address such research questions, the presence of interaction among risk factors can be examined.

Causal interaction between two risk factors is considered most clinically relevant in epidemiology. Causal interaction occurs when two risk factors act together in causing disease and is explicitly defined as a deviation from additivity on a risk difference scale. Statistical interaction can be evaluated on both an additive (absolute risk) and multiplicative (relative risk) scale, depending on the model that is used. When using logistic regression models, which are multiplicative models, several measures of additive interaction are presented to evaluate whether the magnitude of an association differs across subgroups: the Relative excess risk due to interaction (RERI), the Attributable proportion due to interaction (AP) or the Synergy index (S). For a transparent presentation of interaction effects the recent STROBE Statement advices to report the separate effect of each exposure as well as the joint effect compared to the unexposed group as joint reference category to permit evaluation of both additive and multiplicative interaction.

Interaction between exposures

Many clinical epidemiological studies investigate whether an exposure, or risk factor, is causally related to the development or progression of a disease or mortality. It might be of interest to study whether this relation is different in different types of patients. In other words, it might be of interest to study whether the effect of one risk factor on a certain outcome is dependent on the presence of another risk factor. For example, we might want to know whether the observed relation between exposure to life style risk factors and the development of chronic kidney disease differs between men and women.[1] Besides observational studies, randomized clinical trials commonly evaluate whether treatment effects differ across certain subgroups. For example, the Modification of Diet in Renal Disease (MDRD) in 585 patients with nondiabetic kidney disease studied whether effect of a low protein diet intervention on kidney failure and all-cause mortality differed between subgroups of blood pressure assignment, baseline GFR, baseline level of proteinuria, cause of kidney disease, age and sex.[2] To address such research questions, the presence of interaction is examined.

In literature, many terms are being used to indicate interaction, for example joint effect or combined effect, synergy, interdependence, heterogeneity of effects, non-uniformity of effects, effect modification, or plain subgroup analyses. In principle, they all mean the same thing: whether the effect of one risk factor is modified by the value of another risk factor. However, there are two different concepts of interaction that may be distinguished: the theoretical concept of causal interaction and the concept of statistical interaction.[3;4]

The purpose of this paper is to explain how interaction can be evaluated and reported in applied data analysis, and to illustrate to what extent different approaches can result in different answers to a research question.

Causal interaction

Causal interaction is a theoretical concept of causation and is explicitly defined as a deviation from additivity of the absolute effects (risk differences) of the two risk factors under study,[3;5-7] meaning that the combined effect of two exposures is more

or less than the sum of their separate effects. Causal interaction between two risk factors thus occurs when they act together in causing disease, or whenever the effect of one is dependent on the presence of the other.[6] In fact, most causes of disease are dependent on the presence of other risk factors to result in a certain disease. The concept of causal interaction thereby refers to a situation that happens all the time in biology.[3] Sometimes, the term biological interaction has been used when interaction is evaluated on an additive scale. However, it must be noted that an observed interaction effect may have no implications about underlying biological mechanisms. Therefore, instead of the term 'biological interaction' the term 'causal interaction' may be preferred to indicate additive interaction between two risk factors.[8]

The additive scale is commonly used in clinical epidemiology, when numbers of events (for example deaths) are counted and every additional observed event (death) in subjects exposed to two risk factors is intuitively considered as excess, implying interaction. By using absolute risks, additive interaction is considered most clinically relevant because of its potential implications for public health. In example 1 we will first examine the presence of causal interaction.

Example 1. Interaction between chronic kidney disease (CKD) and cardiovascular disease (CVD) *A study explored the interaction between CKD and CVD in the association with a composite outcome of cardiac events, stroke and death in 10 years of follow-up of 26147 individuals from 4 community-based studies.[9] The authors hypothesized that since CKD is a risk factor of CVD while CVD may promote CKD, CKD and CVD might have a synergistic effect on future cardiovascular and mortality outcomes. Table 1 shows the rates of the composite outcome per 1000 person-year.*

Table 1. Rates of composite outcome per 1000 person-year in 26,147 individuals during ten years of follow-up without CKD or CVD, with CKD or CVD or with both CKD and CVD at baseline.[9]

	CKD -	CKD +
CVD -	16.9	44.9
CVD +	52.7	116.4

CKD=Chronic kidney disease, CVD=Cardiovascular disease, -=without exposure, +=with exposure

What can be concluded from Table 1? In persons without CKD and CVD at baseline the rate of the composite outcome was 16.9/1000 person-year (py). This can be considered as the background rate: from all persons without CVD and CKD at baseline, 16.9 per 1000 person-year got a cardiac event or died within ten years. In persons with CKD at baseline this was 44.9/1000 py, resulting in a risk difference of 44.9-16.9= 28/1000 py. This additional 28/1000 py can be considered as purely due to exposure to CKD. In persons with CVD at baseline the rate was 52.7/1000 py, 52.7-16.9=35.8/1000 py more due to exposure to CVD. When no interaction between CKD and CVD would be present, we would expect an outcome rate in persons exposed to both CKD and CVD at baseline of 16.9+28+35.8=80.7/1000 py: 16.9/1000 py will get the outcome anyway, an extra 28/1000 py due to exposure to CKD and an additional 35.8/1000 py due to exposure to CVD. The observed rate, however, was 116.4/1000 py.[9] Thus, the composite outcome occurred in 116.4-80.7= 35.7 persons per 1000 py more than we would expect on the basis of the sum of the separate effects of CVD and CKD, implying the presence of causal interaction between CKD and CVD. In other words, due to interaction between CKD and CVD, an excess risk of 35.7/1000 py has been observed. Although some consider every single extra case a departure from additivity, the clinical relevance of the magnitude of the effect needs of course to be evaluated on the basis of knowledge on the subject matter. Note that in this first example, we evaluated the presence of interaction on the basis of risk differences on an additive scale (the calculation of risk differences was reported in an earlier paper of this series[10]).

Statistical interaction

Statistical interaction refers to the inclusion of a product term of the two risk factors under study in a statistical model, which is explained below. In many studies, the presence of interaction between two risk factors is assessed by testing whether the regression coefficient of such product term is statistically significant, representing the excess risk due to interaction of the exposures. However, in this way, the presence of interaction is tested on the underlying scale of the model. A previous paper in this series explained the applications of linear and logistic models.[11] The following equations show that the underlying scales of these models are different.

The regression equation of the linear regression model including a product term, or interaction term, is

$$E(y) = ß_0 + ß_1X_1 + ß_2X_2 + ß_3X_1X_2$$

Where E(y) is the estimated effect, $ß_0$ is the intercept that can be interpreted as the background risk, $ß_1$ ad $ß_2$ are the regression coefficients of the risk factors X_1 and X_2. By including the product term (X_1 x X_2) the interaction effect is estimated through estimation of the regression coefficient $ß_3$. When for example E(y) represents the mean glomerular filtration rate (GFR), X_1 indicates whether the patient received a certain diet (X_1=1) or not (X_1=0), and X_2 indicates whether patients are men (X_2=1) or women (X_2=0), solving the regression equation in women without the diet would result in GFR= $ß_0$, in women with the diet GFR= $ß_0 + ß_1$, in men without the diet GFR= $ß_0 + ß_2$, and in men with the diet GFR= $ß_0 + ß_1 + ß_2 + ß_3$. A statistically significant interaction effect (when the regression coefficient $ß_3$ tests significant) would mean in this example that the effect on GFR is ($ß_3$) different in men than in women. Because linear regression models are additive models (the effects sum up), the absence of an interaction term in such a model ($ß_3$=0) implies exact additivity of effects (GFR= $ß_0 + ß_1 + ß_2$). A statistically significant regression coefficient of the product term ($ß_3$) indicates a deviation of additivity, implying the presence of interaction on an additive scale.

In contrast, logistic models, including the Cox regression model, are multiplicative models (the effects multiply). The regression equation of the logistic regression model including an interaction term is

$$Ln[p/(1-p)] = ß_0 + ß_1X_1 + ß_2X_2 + ß_3X_1X_2$$

This equation can be rewritten as

$$[p/(1-p)] = e^{ß0 + ß1X1 + ß2X2 + ß3X1X2} = e^{ß0} \times e^{ß1X1} \times e^{ß2X2} \times e^{ß3X1X2}$$

Where [p/(1-p)] is the odds of the outcome. The absence of a product term in such a model ($ß_3$=0) implies a multiplicative relation between the effects ($e^{ß0} \times e^{ß1X1} \times e^{ß2X2}$),

whereas a statistically significant product term between two risk factors implies departure from multiplicativity, rather than from additivity.

Thus, by including a product term in the model, it depends on the model that is used (linear or logistic) whether the interaction effect is tested on an additive (risk difference) or a multiplicative (relative risk) scale. The study of example 1 illustrates how difficult it is to interpret interaction terms in modeling: the variables CKD, CVD and the product term of CKD and CVD were also included in a multivariate Cox regression model. The regression coefficient of the interaction term was not significant and it was concluded that the interrelationship between CKD and prior CVD was only additive,[9] whereas a departure from multiplicativity had been tested.

It must be noted that many studies lack sufficient power to detect interaction effects statistically significant in subgroup analyses. As a result, a p-value higher than 0.05 may not always mean the absence of multiplicative interaction. Furthermore, any absence of departure from multiplicativity does not preclude departure from additivity. Even when relative risks are similar within two subgroups of a risk factor, interaction may be present on an additive scale, especially in case of a strong risk factor like age. The MDRD Study for example did not detect an interaction effect on a multiplicative scale between age and diet (p=0.73 for kidney failure and death) in 585 patients with nondiabetic kidney disease.[2] However, because the mortality rate among older patients is much higher than among younger patients, similar hazard ratios may result in a large risk difference, implying the presence of interaction on an additive scale.

With the crude data of Table 1, the presence of interaction can also be evaluated on a multiplicative, or relative scale. In persons with CKD at baseline the rate of the composite outcome is 2.66 times greater than the background rate (16.9 x 2.66= 44.9 per 1000 py). In persons with CVD at baseline, the rate is 3.12 times greater than the background rate (16.9 x 3.12= 52.7 per 1000 py). On a multiplicative scale the expected rate in the group with both CKD and CVD would be 16.9 x 2.66 x 3.12=140.3 per 1000 py (or, 8.28 times greater than the background rate). Since the observed rate was 116.4/1000 py (only 6.89 times greater than the background

rate), the interaction effect is less than multiplicative. This is also considered as a departure from multiplicativity. However, when the same data were evaluated on a risk difference scale, an excess risk of 35.7/1000 py was detected in patients with both CKD and CVD. The results are depicted on both scales in Figure 1 to illustrate that there is interaction on both an additive and a multiplicative scale. On the basis of the multiplicative scale the combination of CKD and CVD appears protective. However, the multiplicative scale may be obscuring the results since more patients reached the composite outcome than was expected on the basis of the separated risks of CKD and CVD, which may be a clinically relevant finding. Assuming additivity, we will not conclude that there is a protective effect, but that there is an interaction effect of CKD and CVD, resulting in excess cases with the composite outcome.

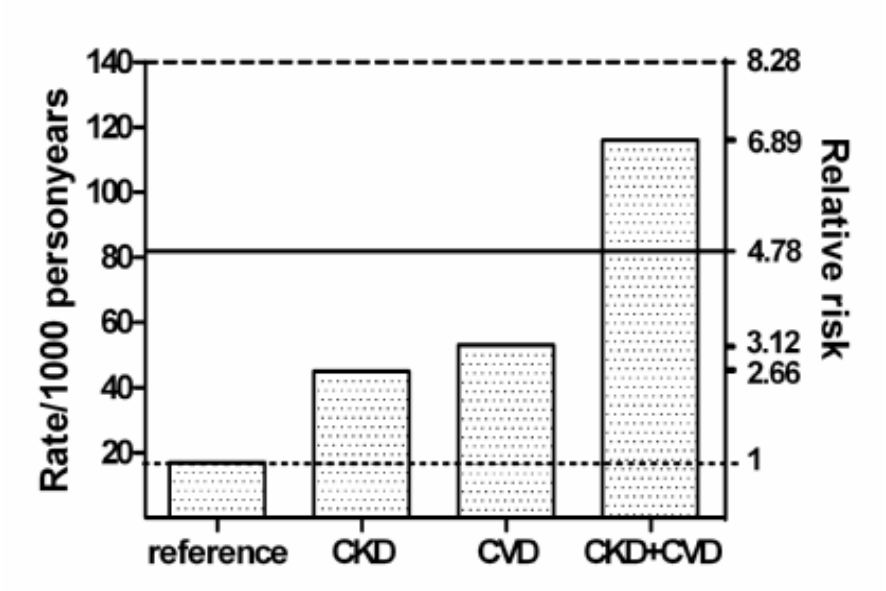

Figure 1. Unadjusted rates of composite outcome per 1000 person-year (left y-axis) and on a relative risk scale (right y-axis) in 26,147 individuals during ten years of follow-up without CKD or CVD, with CKD or CVD or with both CKD and CVD at baseline. The dotted line indicates the background risk (16.9/1000 person-year; RR=1); the straight line indicates exact additivity of effects; the dashed line indicates exact multiplicativity of effects. Since the observed rate of the composite outcome is 116.4/1000 py, there is both a departure from additivity and a less-than-multiplicative effect. CKD=Chronic kidney disease, CVD=Cardiovascular disease.

Measures of additive interaction derived from multiplicative models

Hence, when a product term is needed in a logistic model, interaction is present on a multiplicative scale. Since logistic regression is at this moment the most commonly used model in clinical research, most analyses are performed on a multiplicative scale. Although counterintuitive, several measures have been developed to evaluate interaction on an additive scale, using relative measures of effect derived from statistically multiplicative models.[6] These measures have been developed originally for use in case-control studies, in which the OR is the measure of effect because incidence rates and risk differences can not be estimated.[10]

For the calculations of these measures of additive interaction between two risk factors a new composite variable with four categories must be computed, indicating a category of joint exposure to both risk factors (++), a category of exposure to one of the risk factors only (+- or -+), and the joint reference category of no exposure (background risk, - - or 1). Logistic regression analysis is then used to estimate the ORs using this new indicator variable. The ORs in the formulas below can be replaced by hazard ratios (HR) when using Cox regression models. Three different measures exist to quantify the amount of interaction on an additive scale[6]:

1) the Relative excess risk due to interaction (RERI), which can be interpreted as the risk that is additional to the risk that is expected on the basis of the addition of the ORs under exposure, calculated as the difference between the expected risk and the observed risk: $RERI = OR_{++} - OR_{+-} - OR_{-+} + 1$

2) the Attributable proportion due to interaction (AP), which is interpreted as the proportion of disease or mortality that is due to interaction among persons with both exposures: $AP = RERI/OR_{++}$

3) the Synergy index (S), which can be interpreted as the excess risk from exposure to both exposures when there is interaction relative to the risk from exposure without interaction: $S = [OR_{++} - 1]/[(OR_{+-} - 1) + (OR_{-+} - 1)]$

In the absence of an interaction effect, RERI and AP equal 0 and S equals 1.

For the purpose of the example we provide the calculations of these measures of additive interaction with the crude relative risks provided in figure 1:

The RERI would be 6.89-2.66-3.12+1= 1.11, the AP 1.11/6.89= 0.16, and the synergy index 5.89/(1.66+2.12)= 1.56. When examining the presence of additive interaction with adjusted hazard ratios or odds ratios, the synergy index should be the measure of choice (indicated below). Although some consider every departure from 0 (RERI and AP) or 1 (S) as evidence for the presence of interaction, there are several possibilities to calculate confidence intervals around these measures of interaction.[12-15] Whereas we focus here on dichotomous risk factors (for example, the presence or absence of CKD), a recent paper provided the methods to estimate interaction on an additive scale between continuous risk factors (for example, age in years) in a logistic regression model.[14]

In practice, the estimation of these measures is straightforward. However, several considerations need to be taken into account when using these measures in the examination of interaction on an additive scale. First, the RERI, AP and S depend on the chosen reference category. In general, this should be the unexposed group as joint reference category (for example, the group without CKD and CVD at baseline). For some variables it may not always be obvious which category to choose as joint reference (for example, men or women, young or old?). Because the measures are difficult to interpret when effects are protective (when the OR of one of the risk factors is below 1) they are best calculated with non-protective effects, e.g. the lowest risk should be chosen as the joint reference category, resulting in a positive risk difference.[6] Second, RERI and AP are not straightforward to interpret after including covariates in the models to control for confounding.[16;17] The problem is that RERI and AP vary across strata defined by covariates, whereas the fundamental interaction parameter is unvarying. For example, after adjustment for sex in example 1, the RERI for interaction between CKD and CVD may differ when calculated separately for men and women. In contrast, the Synergy index does not vary across strata, which suggests that it is the measure of choice in multivariate models.[16] Third, similar to the OR, one should realize that the RERI, AP and S based on logistic regression only approximate the true measures in closed cohorts.[16;18;19] Finally, certain data may better statistically fit additive or multiplicative models. It may seem counterintuitive when variables are modelled on a multiplicative scale, that two risk factors are selected to be examined on an additive scale. However, for

a causal interpretation, the presence of interaction needs to be examined on an additive (risk difference) scale.[3;6]

Recommendation for reporting of interaction

In order to prevent confusion and ambiguous conclusions the presentation of the methods and results must clarify which method and scale the authors have used to evaluate the presence of interaction in their research.[4] Papers that include subgroup analyses commonly report p-values of included product terms in logistic regression models and stratified results (per subgroup) when p-values are significant. This reporting is insufficient for the reader to evaluate whether there is departure from additivity when one wants to communicate a causal interaction effect.

Example 2. Interaction between age and treatment

The Dialysis Clinical Outcomes Revisited (DCOR) trial is a randomized trial of sevelamer compared to calcium-based phosphate binders in 1068 prevalent hemodialysis patients.[20] A significant interaction effect between age and treatment (p=0.02) was detected in relation to all-cause mortality and hazard ratios were reported separately for younger patients (<65 years) (HR:1.18, 95% ci: 0.91-1.53) and older patients (≥65 years) patients (HR:0.77, 95% ci: 0.61-0.96).

With these results only, the presence of interaction can not be evaluated on an additive scale. Because the mortality rates of each exposure group were also reported we are, however, able to interpret the interaction effect on an additive level. The mortality rate in younger patients on calcium-containing binders was 10.6 per 100 patient-year, 12.5/100 py in younger patients on sevelamer, and 23.4/100 py in older patients on calcium-containing binders.[20] On the basis of the effect of sevelamer in younger patients we would expect a mortality rate of 25.3/100 py in older patients on sevelamer. However, the observed mortality rate was 18.3/100 py, representing an interaction effect of 7 deaths per 100 patient-year less than expected on the basis of the separate effects of older age and sevelamer.

The recent STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement advices a transparent presentation of the separate effect of

each exposure as well as the joint effect, each relative to the unexposed group as (joint) reference.[21] Such a variable with the four possible exposure categories will give the reader sufficient information to evaluate both additive and multiplicative interaction.[21] The results in the following example permit evaluation of different scales of interaction.

Example 3. Interaction between renal dysfunction and impaired fasting glucose (IFG) *This study in 9918 participants in an antihypertensive treatment program examined the presence of interaction of moderate renal dysfunction (MRD) and IFG upon the risk of ischemic heart disease (IHD) mortality.[22] The authors reported that the interaction product term of MRD and IFG significantly improved (P=0.001) a Cox regression model. Since the regression coefficient of the product term was not given, the magnitude and the direction of the interaction effect can not be concluded from this information only. However, the authors furthermore report absolute mortality rates for persons with normal and impaired fasting glucose within each group of renal dysfunction, and the hazard ratios from a Cox model for those with IFG only (HR, 95%-CI: 1.48, 1.10-2.00), MRD only (1.69, 1.16-2.46), and both IFG and MRD (0.71, 0.36-1.43), with the reference being neither IFG or MRD.[22]*

These HRs can be used to calculate for example the RERI (RERI=0.71-1.69-1.48 +1=-1.46; indicating that because of interaction between IFG and MRD, the hazard ratio was 1.46 lower than expected from the addition of the separate effects of IFG and MRD). The authors herewith provide the reader with sufficient information to evaluate the presence of interaction on both an additive and multiplicative scale. In contrast to prior expectations, renal dysfunction seemed to protect hypertensive patients with impaired fasting glucose from mortality due to IHD. The authors are cautious in the interpretation of this effect since their finding was unanticipated and warrant further study.[22]

CONCLUSION

In summary, many terms to indicate interaction exist. For a causal interpretation interaction is measured on an additive scale. When using product terms in statistical models one should consider whether the underlying scale of the model is additive, or multiplicative. When using logistic regression models, measures of additive interaction can be used to evaluate whether the magnitude of an association differs across subgroups. For a transparent presentation of interaction effects the recent STROBE Statement advices to report the separate effect of each exposure as well as the joint effect compared to the joint reference category to permit evaluation of both additive and multiplicative interaction.

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