Progression of CKD form pre-dialysis : natural course, risk factors, and outcomes

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Chapter 3 |

Reporting of interaction

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Abstract

Interaction is the situation whereby the association of one risk factor with a certain outcome variable differs across strata of another risk factor. From a public health perspective, the assessment of interaction on an additive scale may be most relevant. Although additive models exist, logistic and Cox regression models are the most commonly used models in epidemiology. The resulting relative risks can be translated to an additive scale. The present paper presents surrogate measures to evaluate the presence of additive interaction when dealing with data on a multiplicative scale (relative risks). For a transparent presentation of interaction effects it is recommended to report the separate effect of each exposure as well as their joint effect compared to the unexposed group as joint reference category to permit evaluation of interaction on both an additive and multiplicative scale.

Introduction

Interaction between risk factors

Interaction is the situation whereby the association of one risk factor with a certain outcome variable differs across strata of another risk factor.[1;2] From a public health perspective, the assessment of interaction on an additive scale may be most relevant.[1;2] An accompanying paper shows how interaction can be examined as departure from additivity using incidence rates.

Although additive models exist, logistic and Cox regression models are the most commonly used models in epidemiology. Furthermore, the case-control study design inherently leads to multiplicative modeling. Consequently, the majority of analyses of epidemiologic data are performed on a multiplicative scale. The resulting relative risks or rate ratios, however, can be translated to an additive scale.

The aim of this paper is to recommend a transparent presentation of interaction effects and to present surrogate measures that can be used to evaluate interaction on an additive scale, using effect measures derived from multiplicative models.

Reporting of interaction

Because the presence of interaction and its interpretation depend on the underlying scale of the statistical model that is used,[3;4] the presentation of the methods and results must clarify which statistical model and scale the authors have used to evaluate the presence of interaction in their research. For a transparent presentation of interaction effects it is recommended to report the separate effect of each exposure as well as the joint effect, each relative to the unexposed group as joint reference category (as shown in Tables 1 and 2).[5;6] Such a two-by-four table will provide the reader with sufficient information to evaluate the presence of interaction on both an additive and multiplicative scale.[6] Botto and Khoury[5] summarized the advantages of such a table for data presentation. If possible, it is recommended to report absolute risks or rates as well.

Table 1. Mortality rates (MR, per 1000 person-year) for all-cause mortality in incident dialysis patients with inflammation (hsCRP>10), a deletion in the pro-inflammatory CC-chemokine receptor 5 gene (CCR5Δ32) or a combination of both.*

Inflammation	CCR5Δ32	MR	Expected MR, assuming additivity	Expected MR, assuming multiplicativity
Yes	Yes	133	227[a]	225[b]
Yes	No	228		
No	Yes	90		
No	No	91		

*Modified from Muntinghe et al[7]; [a]calculated as: background rate + effect of inflammation + effect of CCR5Δ32 = 91 + (228-91) + (90-91) = 227; [b]calculated as: relative effect of presence of inflammation * relative effect of CCR5Δ32 * background rate = (228/91) * (90/91) * 91 = 225.

Measures of additive interaction derived from multiplicative models

Three measures have been devised by Rothman[2] to evaluate additive interaction using effect measures derived from multiplicative models, such as logistic or Cox regression models.[8] These are the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S).[2;8] To calculate these measures, a simple logistic or Cox regression model should be built. This model should include a new composite variable, containing four expo-sure categories. The four categories indicate (1) the reference category (background risk; no exposure, or --), (2) a category for exposure to one of the risk factors under study (-+), (3) a category for exposure to the other risk factor to be examined (+-), and (4) a category for joint exposure to both risk factors under study (++).[3;8;9] Subsequently, the measures to evaluate additive interaction in relative risk data[3;8-11] can be calculated as follows ('RR', relative risk, refers to either odds ratio in a logistic regression model or hazard ratio in a Cox regression model):

(a) RERI = $RR_{++} - RR_{+-} - RR_{-+} + 1$. RERI can be interpreted as the extra risk due to interaction calculated as the difference between the (expected) effect based on the summation of the separate effects of the two risk factors under study and the (observed) effect in the joint exposure category.
(b) AP = $RERI/RR_{++}$. AP can be interpreted as the proportion of the events under study (e.g. disease or mortality) that is due to interaction among persons with both exposures. AP is often expressed as a percentage.
(c) S = $(RR_{++} - 1)/([RR_{+-} - 1] + [RR_{-+} - 1])$. S can be interpreted as the excess risk from exposure to both risk factors when interaction is present, relative to the risk from exposure when interaction is absent.

When additive interaction is absent, both RERI and AP are equal to 0 and S is equal to 1. In practice, the indices will hardly ever be exactly 0 or 1. The associated 95% confidence interval (CI) may help in deciding whether additive interaction is absent (if 0 is clearly within the 95% CI of RERI and AP or 1 is clearly within the 95% CI of S). Several methods to calculate CIs around RERI, AP, and S have been proposed. Details, including Excel sheets for calculation, can be found elsewhere.[9;10;12-14]

The reference category should be the category with the lowest risk, since RERI, AP, and S are difficult to interpret when effects are protective.[2] It is possible to include additional terms to control for confounding in the statistical model. However, in contrast to S, RERI and AP may vary across strata defined by covariates.[11] Therefore, although some advocate RERI as the best choice of measures of additivity,[15] S seems the measure of choice in assessing the presence of additive interaction in multivariate models.[11]

Example with hazard ratios

In a study on the effects of soluble TNF-like weak inducer of apoptosis (sTWEAK) plasma levels on mortality, the interaction effect between sTWEAK levels and the presence of inflammation in hemodialysis patients were investigated.[16] The authors conclude, based on RERI 2.0 (95% CI –0.3 to 4.3), AP (43%), and S 2.2 (95% CI 0.8 to 5.9), that high sTWEAK levels have more than additive effects on all-cause mortality in hemodialysis patients with inflammation. Table 2 provides the underlying hazard ratios and the calculation of the measures.

Table 2. Hazard ratios for all-cause mortality with 95% confidence interval (CI) in 218 hemodialysis patients with inflammation (high IL-6 levels), high soluble TNF-like weak inducer of apoptosis (sTWEAK) levels, or a combination of both.*

Inflammation	High sTWEAK levels†	Hazard ratio (95% CI)
Yes	Yes	4.72 (2.24 to 9.94)
Yes	No	2.70 (1.36 to 5.38)
No	Yes	0.99 (0.37 to 2.61)
No	No	1 (reference)

*Modified from Carrero et al[16], †high sTWEAK was defined as above the 66th percentile. The three measures of additive interaction can be calculated as follows:

$RERI = RR_{+\,+} - RR_{+\,-} - RR_{-\,+} + 1 = 4.72 - 2.70 - 0.99 + 1 = 2.0$;

$AP = RERI/RR_{+\,+} = 2.0/4.72 = 0.43 = 43\%$;

$S = (RR_{+\,+} - 1)/([RR_{+\,-} - 1] + [RR_{-\,+} - 1]) = (4.72 - 1)/([2.70 - 1] + [0.99 - 1]) = 2.2$.

Implication of additive interaction

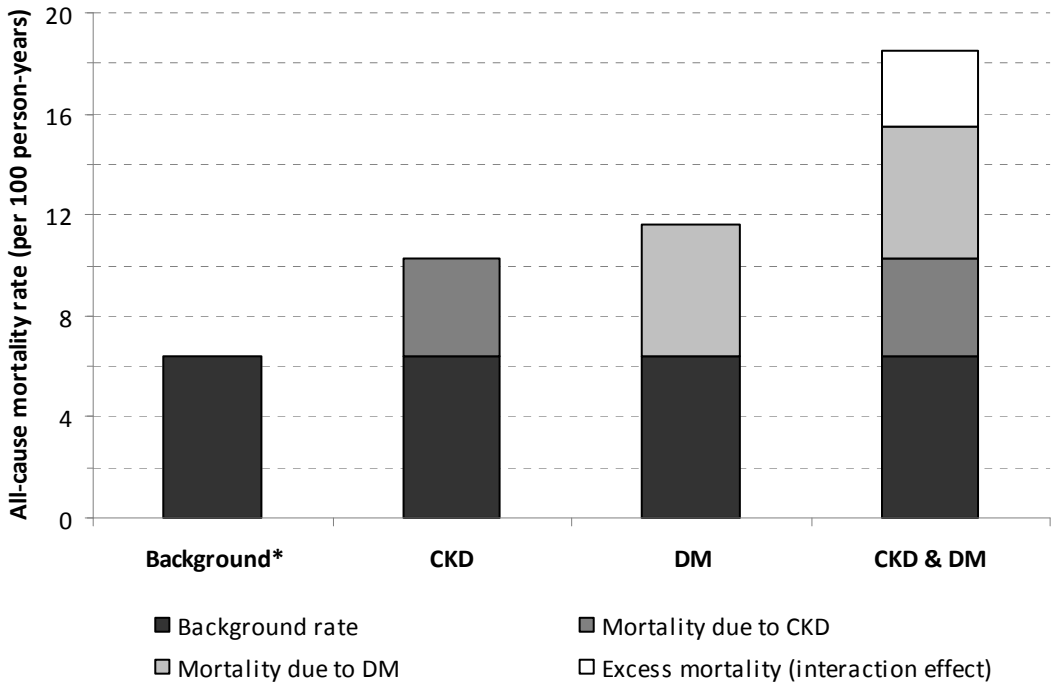
The joint effect of chronic kidney disease (CKD) and diabetes mellitus (DM) in the association with all-cause mortality was assessed in a cohort study of 19,737 individuals being at high risk for (first) myocardial infarction or who had previous acute coronary syndromes together with average cholesterol levels.[17] The all-cause mortality rate was lowest in subjects without both CKD and DM (background rate of 6.4/100 person-years, py) (Figure 1). The mortality rate in subjects with CKD (background rate + additional effect of CKD of 3.9/100py) was slightly increased. Likewise, the mortality rate in subjects with DM (background rate + additional effect of DM of 5.2/100py) was increased. On top of the combined effect of background, CKD, and DM an additional effect was present. This excess effect of 3/100py is called the interaction effect. Assuming causality, this implies that if the occurrence of CKD could be prevented in this population, this would not only prevent the 3.9 cases per 100py, but in addition the 3 cases per 100py (i.e. in total 7 deaths in 100 persons that are followed for 1 year) would be prevented that would have occurred because of interaction between CKD and DM.

Conclusion

Measures of additive interaction (RERI, AP, S) can be derived from multiplicative models to examine the presence of interaction on an additive scale using relative risks. For a transparent presentation of interaction effects it is recommended to report the separate effect of each

exposure as well as their joint effect, each relative to the joint reference category to permit evaluation of the presence of interaction on both an additive and multiplicative scale.

Figure 1. All-cause mortality rates per 100 person-years in 19,737 patients with chronic kidney disease (CKD), diabetes mellitus (DM), or a combination of both. The median follow-up period for all patients was 64 months.*



*Modified from Tonelli et al[17], †Background means all-cause mortality rate in patients without CKD, DM, or both

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