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Visualizing interaction effects: a proposal for presentation and interpretation

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Abstract

Objective: Interaction terms are often included in regression models to test whether the impact of one variable on the outcome is modified by another variable. However, the interpretation of these models is often not clear. We propose several graphical presentations and corresponding statistical tests alleviating the interpretation of interaction effects.

Study Design and Setting: We implemented functions in the statistical program R that can be used on interaction terms in linear, logistic, and Cox Proportional Hazards models. Survival data were simulated to show the functionalities of our proposed graphical visualization methods.

Results: The mutual modifying effect of the interaction term is grasped by our presented figures and methods: the combined effect of both continuous variables is shown by a two-dimensional surface mimicking a 3D-Plot. Furthermore, significance regions were calculated for the two variables involved in the interaction term, answering the question for which values of one variable the effect of the other variable significantly differs from zero and vice versa.

Conclusion: We propose several graphical visualization methods to ease the interpretation of interaction effects making arbitrary categorizations unnecessary. With these approaches, researchers and clinicians are equipped with the necessary information to assess the clinical relevance and implications of interaction effects.

Keywords: Interaction; Visualization; Categorization; Cox models; Linear models; Logistic models

1. Background

In epidemiology, interaction terms are often incorporated into multivariable regression models to test whether the impact of one variable on the outcome is modified by another variable. However, the interpretation of interaction effects is often not clear. It depends on the scale of the variables included in the interaction term (continuous and/or categorical) and the scale of the model (linear regression, logistic regression, Cox Proportional Hazards model). The interpretation is rather straightforward, if interaction effects between the two categorical variables or between one continuous and one categorical variable are considered. One such example would be an effect that can only be seen in men, but not in women, in Europeans but not in Asians etc. For such situations, there are also graphical solutions implemented in standard statistical programs [1]. If researchers are interested in interaction between two continuous variables, the interpretation is less clear. It seems that interaction terms between continuous variables are avoided or continuous variables are categorized beforehand. If significant *P*-values of continuous interaction terms are reported, most authors switch to categorizations of these former continuous variables for interpretation purposes. In general, categorizations of continuous variables are often done rather arbitrarily by choosing percentiles of the respective interacting variables, for example, by dichotomizing using the median [2]. Categorization of continuous variables leads to significant loss of information and power, though [3]. Sometimes, clinically recognized and predefined cutpoints are chosen, such as a body mass index of >30 kg/m^2 for the definition of obesity. Even in this case, information is lost because the definition of these cutpoints has been designed for a totally different purpose. This approach can lead to considerable bias. The problem even worsens, if both continuous variables that constitute to an interaction term are categorized [4].

In other cases, regression coefficients and *P*-values of interaction terms are shown, but the reader is left alone with the

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What is new?

1. Epidemiological publications on interaction effects in survival analyses mostly use categorizations of variables for the ease of interpretation. This approach might lead to considerable bias, though.
2. To ease the interpretation of interaction effects between two continuous variables, we propose a graphical visualization approach which we implemented in functions in the statistical program R. They can be used on Generalized Linear Models and Cox Proportional Hazards models.
3. The mutual modifying effect of both variables constituting the interaction effect can be shown by a two-dimensional twisted surface and interaction plots showing the effect estimator of one variable for varying values of the other variable.

interpretation. The effects and *P*-values of the main effects are also not interpretable without taking into account the concurrent levels of the other constituting variable [5].

By including multiplicative interaction terms, conditional hypotheses are tested: An increase in one variable is associated with an increase in the outcome variable, when the second interacting variable is equal to a specific value. Inevitably, all constitutive terms of an interaction term should be included in the regression model also individually. With the inclusion of an interaction term, these former average effects are conditional effects then and change just by definition. Therefore, changes in effects and/or *P*-values after including interaction terms cannot be interpreted usefully. The conditional nature also applies for the *P*-values of the conditional effects, which are given in the output tables of statistical programs: they test, whether the slope of one variable is significantly different from zero, if the other constituting variable is zero. In most cases, this test is not very useful, depending on the scale of the variable.

The typical reader will not make the necessary linear combinations to calculate the effect of the first variable for specific values of the second variable. It would be possible, though, given the typical output table of a regression model, including effect estimates, standard errors, and *P*-values. However, it is not possible to conclude on the statistical significance of such a linear combination.

Therefore, it is hardly possible to interpret interaction effects simply by looking at the output table from regression models. The results of interaction terms have to be presented in a different, more reader-friendly way.

Such examples can only rarely be found. We conducted a literature search on survival analyses publications including interaction terms between two continuous variables (see Appendix on the journal's Web site at www.jclinepi.com). It revealed that only one study group used the complete range of both continuous variables to interpret the interaction effects: The authors presented interaction plots, showing the modifying effect of waist circumference on the relationship between several parameters (cholesterol, leptin, and adiponectin) and mortality [6,7].

The lack of such forms of presentations is certainly because of unfamiliarity with the methodological background and lack of easy to use methods. Therefore, such methods are required in the clinical epidemiological setting to avoid common misinterpretations in interaction models.

To ease the interpretation of interaction effects between two continuous variables, we propose several possibilities for graphical presentation, which we implemented in functions in the statistical program R: These functions have been implemented for linear regression, logistic regression, and Cox Proportional Hazards models. To demonstrate the functionalities, one data set including survival data has been simulated and analyzed in Cox models including linear interaction effects between two continuous predictors.

2. Methods

2.1. Formulating and interpreting multiplicative interaction terms in linear, logistic, and Cox models

For explanatory purposes, a linear regression model is assumed first. Interaction terms between two continuous variables x_1 and x_2 on the continuous outcome variable Y can be modeled in the following way:

$$E(Y|x_1,x_2) = X\beta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 (x_1 * x_2) \quad (1)$$

with β_0 being the intercept, β_1 and β_2 the conditional effects of x_1 and x_2 and β_3 being the interaction effect on the outcome *Y*. The linear combination on the right side of the equation is the linear predictor $X\beta$, to which further covariates can be added. The regression coefficients for x_1 and x_2 are conditional effects because they depend on the values of the other constituting variable:

A one unit change of x_1 corresponds to a change of $\beta_1 + \beta_3 x_2$ on *Y*.

A one unit change of x_2 corresponds to a change of $\beta_2 + \beta_3 x_1$ on *Y*.

This means that β_1 itself is the effect of x_1 on *Y*, if x_2 is equal to zero and vice versa. Thus, the interpretation of regression coefficients cannot be done without taking the levels of the interacting variable into account. According to Rothman [8], the statistical term " interaction" is used to refer to departure from the underlying form of a statistical model. For a linear model, a significant interaction term thus implies deviation from additivity, meaning the additive effect of the individual effects $\beta_1 x_1 + \beta_2 x_2$ on the outcome.

The interpretation based on the direction of effect estimates is only unambiguous, if both the conditional effect, for example of x_1, and the interaction effect have the same effect direction. In this case, the absolute value of the overall x_1 effect increases for increasing values of x_2. If all effect estimates are positive, this implies that the interaction leads to more than an additive effect. If the interaction effect and conditional effect have opposing algebraic signs, the conditional effect is attenuated by increasing values of the other interacting variable and can even be switched into the other direction, depending on the size of the corresponding estimates. Obviously, interpretation of interaction effects based on the table of regression coefficients alone is hard to accomplish and requires at least some linear combinations to be made.

The corresponding *P*-values are interpreted accordingly: They also reflect the x_1 effect on Y for $x_2 = 0$ and vice versa. This may or may not be useful depending on the scale and ranges of the variables. One may want to test, however, whether the effect of x_1 significantly differs from zero given a specific value of x_2. The equation for this ''simple slopes test'' requires the regression coefficients to be known and the corresponding variance-covariance matrix [5], which can be given by the estimated regression model.

If you want to test the effect of x_1 for a specific x_2 value, the slope to be tested would be given by:

$$\text{slope}(x_1) = \beta_1 + \beta_3 x_2 \tag{2}$$

and the corresponding standard error by

$$\text{se}_{\text{slope}(x_1)} = \sqrt{s_{11} + 2 * x_2 s_{13} + x_2 s_{33}} \tag{3}$$

with s_{11} being the variance of β_1, s_{33} the variance of β_3, and s_{13} the covariance of β_1 and β_3.

Given the slope and its standard error, a *t*-test can then be constructed:

$$t = \frac{\text{slope}(x_1)}{\text{se}_{\text{slope}(x_1)}} \sim t(n-k-1) \tag{4}$$

with n being the number of cases and k the number of variables not including the intercept. The simple slopes test of x_2 effects for specific x_1 values can be derived likewise.

The interpretations and formulas on effect estimates given in this paragraph can be generalized to logistic regression or Cox models by substituting the expectation of the outcome variable by a general function. The linear predictor $X\beta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 (x_1 * x_2)$ is then modeled by a monotone link function as the logit function $\ln(p/(1-p))$ for logistic regression models, with p being the probability of the outcome. In this case, the intuitive effect measure is the odds ratio (OR), which is estimated by $\text{OR}_i = \exp(\beta_i)$ for variable x_i. Thus, the regression function can be rewritten to $p/1 - p = \exp(\beta_0) * \exp(\beta_1 x_1) * \exp(\beta_2 x_2) * \exp(\beta_3 (x_1 * x_2))$. On this scale, a significant interaction effect would imply a deviation from multiplicativity of individual effects [9], in contrast to interaction effects in a linear model, which shows departure from additivity.

The Cox Proportional Hazards model [10] models the time to a specific event such as death accounting for censored observation. The hazard function $h(t)$ is the instantaneous probability of an event at time t given that the individual has survived until time t and is defined as follows:

$$h(t) = h_0(t)\exp(X\beta) \tag{5}$$

with $h_0(t)$ being the underlying baseline hazard, which cannot be estimated. For each of the covariates in the linear predictor, the factor $\exp(\beta_i)$ gives the so-called hazard ratio (HR), which is a measure of relative risk. It characterizes the shift in the hazard function as a result of a shift of one unit in the corresponding variable x_i. The interpretation on interaction effects on the linear predictor $X\beta$ in a Cox model can be done analogical to the linear regression model. For Cox models, it might be more meaningful to look at the change in HR, though. As for logistic regression models, on the scale of the relative risk estimate, the inclusion of interaction terms tests the deviation from multiplicativity.

2.2. Description of the simulated survival data set including interaction effects

We simulated survival data to explain the interpretation of interaction effects and show the utilities of our graphical presentations in a Cox model. One thousand right-censored observations were generated with three continuous and normally distributed variables with mean 0 and variance 1. In addition, one $N(0,1)$-distributed nuisance parameter has been included, that is ignored in the following Cox model. Therefore, the linear predictor was constructed as follows:

$$\text{Linear predictor } X\beta = -2 * x_1 + 0 * x_2 + 1 * (x_1 * x_2) + 1 * x_3 + N(0,1)$$

The effect estimates were chosen to represent two possible interaction scenarios: a strong main effect that attenuates for increasing values of the other interacting variable is reflected by β_1, whereas $\beta_2 = 0$ reflects an effect, that would not be observed in a model not including an interaction term because the x_2 effect even changes direction for varying values of x_1.

The simulation was performed using function ''Simsurv'' of the library ''prodlim'' in R [11]. For each observation, a Weibull distributed survival time was generated with baseline risk set to 0.2. The censoring time was simulated to follow an exponential distribution with a baseline censoring risk set to 3. The baseline risks for censoring and survival were chosen to yield a high censoring rate. The minimum of the two simulated times was taken as observation time. The event indicator was set to 1, if the survival time was shorter than the censoring time, otherwise the indicator was set to 0.

2.3. Implementation of the graphical utilities and calculations in R

Several functions have been implemented in R to alleviate the interpretation of multiplicative interaction effects. They can be downloaded from http://www3.i-med.ac.at/genepi/ under "Analysis tools." First, a generalized linear model (GLM) or Cox model has to be fitted using the function glm or cph (from the Design library). Then, the function PlotInteraction3D (or PlotInteraction3DCox) calculates predicted values of the linear predictor for either the GLM or Cox model for given ranges of both variables constituting the interaction term. Additional covariates and also factor variables can be included in the models. By default, mean values are chosen for continuous covariates. For the factor variables, one factor level has to be chosen, for which predicted values should be calculated. The resulting matrix of predicted values is spanned as a two-dimensional surface into a three-dimensional grid. Alternatively, a colored contour plot can be given out. Consecutively, two-dimensional slices can be cut out of this plot for specific values of one of the constituting variables (function "PlotInteraction2D"). Each slice is the linear predictor of the regression model for varying values of one variable keeping the other variable fixed. Assuming a linear model, for example, this corresponds to the predicted outcome. Setting x_2 to the fixed value c, it can be derived from formula (1) by $y=\beta_0+\beta_1 x_1+\beta_2 c+\beta_3 c x_1$. The function "PlotInteraction2D" uses the R-function "predict," which gives out these fitted values and the corresponding standard errors (*se.fit*). In addition, point-wise 95% confidence intervals are calculated for each value of, for example, x_1 by $y \pm z_{0.975} * se.fit$, which are plotted for the complete range of x_1 values, with $z_{0.975}$ being the 97.5% quantile of the normal distribution (~1.96). It is recommended to look at those plots for a set of values spanning the range of the variable, for example, for the 5th, 25th, 50th, 75th, and 95th quantile. By means of the functions "getRegion" or "getRegionCox," significance regions can be calculated. For a given range of values for x_1, for example, the slope of the x_2 variable with the corresponding *P*-value is printed. An interaction effect plot [12] is also given out, which shows how the effect of one variable changes with the changing values of the other variable. This corresponds to plotting the effect estimate of one variable ($\text{slope}(x_1)$) for a given value of the other variable as in formula (1). The respective point-wise 95% confidence intervals for the x_1 effects for given values of x_2 are derived from (1) and (2) by $\text{slope}(x_1) \pm z_{0.975} * \text{se}_{\text{slope}(x_1)}$. Both, effect estimates for x_1 and corresponding confidence intervals are plotted for varying values of x_2 over their complete range. For logistic and Cox models, OR or HR can be given alternatively by exponentiating the effect estimates and the corresponding confidence intervals. Thus, two figures, one for each of the two interacting variables, are sufficient to summarize the interaction effect over the complete range of both continuous variables.

3. Results

Eighty-two percent of the simulated observations are censored. The results of the simulated Cox model are given in Table 1. The risk experiencing an event is significantly decreasing for increasing values of x_1 (HR = 0.1521, $P < 0.001$), if $x_2 = 0$. If $x_1 = 0$, x_2 does not have an effect on the hazard. Other implications that can directly be drawn from the numbers in the table, are that there is a significant interaction effect, meaning, that the effects of x_1 and x_2 vary for varying values of the other variable. Other slopes can be calculated by linear combinations of the effect estimates: The effect estimate of x_2 for specific x_1 values can be calculated by $0.0227 + 1.0378*(x_1 \text{ value})$. For $x_1 = -0.6456$ (=25% quantile), this would be −0.6473, for $x_1 = 1.772$ (=95% quantile), it is 1.862. For the calculation of *P*-values, however, specific covariances are needed from the output of the model. Thus, they cannot be derived directly from Table 1, but can be given out by applying the test given in formula (4) implemented in the function "getRegionCox": $P = 4.4e-14$ (for $x_1 = -0.6456$) and $P < 10e-20$ (for $x_1 = 1.772$).

A rough overview of the impact of the interaction can be given by the twisted surface in Fig. 1: The highest risk can be found at consecutive low values of both variables. The variable x_1 does have a negative impact on the risk for low values of x_2. For increasing values of x_2, the x_1 effect is attenuated. For low values of x_1, the variable x_2 is positively associated with the outcome variable, which is time to event in this example (increasing slope), whereas x_2 is inversely associated for high values of x_1 (decreasing slope). The surface is twisted, indicating that the direction of the x_2 effect even changes direction for varying values of x_1. Alternatively, a colored contour plot (Fig. 2) can depict the same information: The highest risk can be found in areas, which are displayed in pink (both x_1 and x_2 low), whereas the risk decreases for darkening blue color.

Fig. 3 shows slices through the three-dimensional plot for specific values of x_1 or x_2. The left panel shows the x_1

Table 1. True and estimated effect estimates of the conditional and interaction effects in the simulated Cox model

Variable	True effect, β	Estimated effect, $\hat{\beta}$	se $(\hat{\beta})$	HR	95% CI of HR	*P*-value
x_1	−2	−1.8834	0.1092	0.1521	[0.1228; 0.1884]	<0.001
x_2	0	0.0227	0.0976	1.023	[0.8449; 1.2386]	0.816
$x_1 * x_2$	1	1.0378	0.0883	2.823	[2.3744; 3.3564]	<0.001
x_3	1	0.8826	0.0777	2.417	[2.0757; 2.8148]	<0.001

Abbreviations: HR, hazard ration; CI, confidence interval.

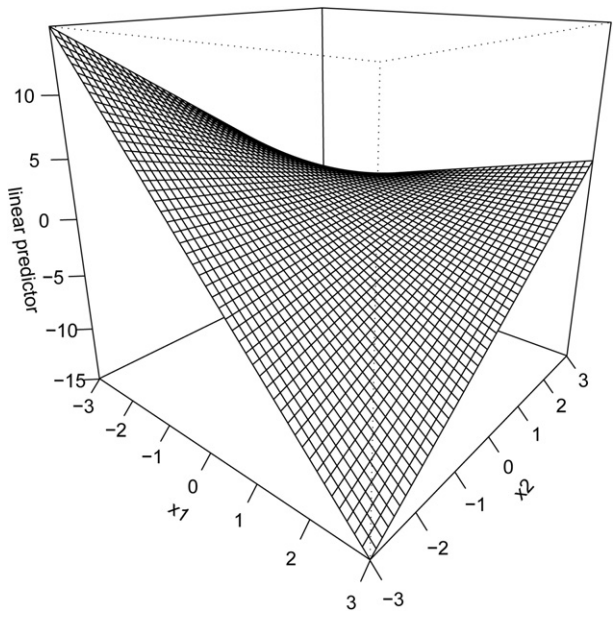

Fig. 1. Interaction surface plot on the linear predictor of the hazard function. The *z*-axis shows the linear predictor of the hazard function for varying values of x_1 and x_2, illustrating their interacting effect on the simulated event variable.

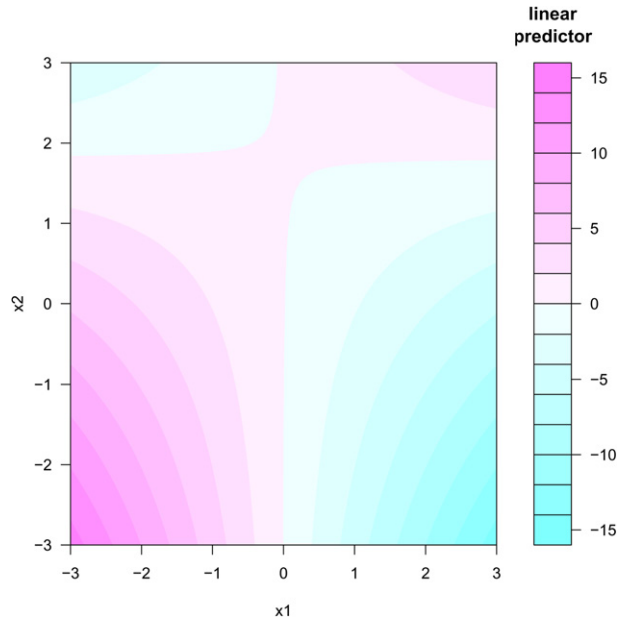

Fig. 2. Contour plot displaying the linear predictor of the hazard function. The linear predictor of the hazard function for varying values of x_1 and x_2 is displayed in different colors, ranging from blue (low risk) to pink (high risk).

effect, given x_2 is equal to the 5th, 25th, 75th, and 95th quantile with its corresponding confidence intervals. The right panel shows the x_2 effects for the same given values of x_1. These plots give the impression of flipping through a flip book, showing the twisting of effects in mutual dependence of the other constituting variable. Significance regions can be given out by the function "getRegionCox." The x_1 effect is significantly different from zero for x_2 values ≤ 1.55 (=94.1% quantile). The x_2 effect is significantly different from zero with a negative slope for x_1 values < -0.19 (=42.16% quantile) and significantly different from zero with a positive slope for x_1 values > 0.17 (=55.9% quantile). The interaction plots in Fig. 4 show the HRs for x_1 for varying x_2 values with pointwise confidence intervals for each plotted value. It can be seen that the HR is significantly lower than 1 for the vast majority of x_2 values. The significance region can also be read from this plot. The x_2 effect changes from an HR that is smaller than 1 to higher than 1 almost exactly at the median of x_1 values. This plot can be printed for the linear predictor, which is the default option, but also for the HR, which has been chosen here in this example.

4. Discussion

We have implemented functions in R providing several different graphical presentations and corresponding statistical tests to ease the interpretation of interaction effects between continuous variables. We have successfully applied one of these approaches in a prospective study on incident dialysis patients, which was very useful for the interpretation of an interaction effect: we observed a significant interaction between time-varying values of albumin and phosphorus on overall mortality in our cohort [13]: for high albumin values, increasing phosphorus concentrations were significantly associated with an increased mortality risk, whereas the beneficial effect of increasing albumin values was only observed for low phosphorus levels. We concluded that decisions about phosphorus-lowering therapy should also take albumin values into account and epidemiological studies and guidelines should consider this interplay. The proposed graphical presentation and the calculation of the significance regions helped in the discussion with clinicians and interpretation of results.

4.1. Categorizing continuous variables in interaction terms: pros and cons

Most of the interaction models between continuous variables that are reported are broken down to subgroup analysis and/or categorizations of at least one of the two continuous variables. A qualitative assessment of epidemiological publications [2] found that 86% of papers evaluating continuous risk factors on health outcomes categorize these risk factors. Most of them use quantiles, others equally spaced categories (e.g., 10-year-age categories) or external criteria, such as clinically respected cutpoints. The reasons for the categorization approaches were not mentioned in most of the publications. There seems to be a gap between statistical capabilities and the ability to interpret interaction effects in a meaningful way. Therefore, simplicity of interpretation might be the most crucial point. However, this simplicity is

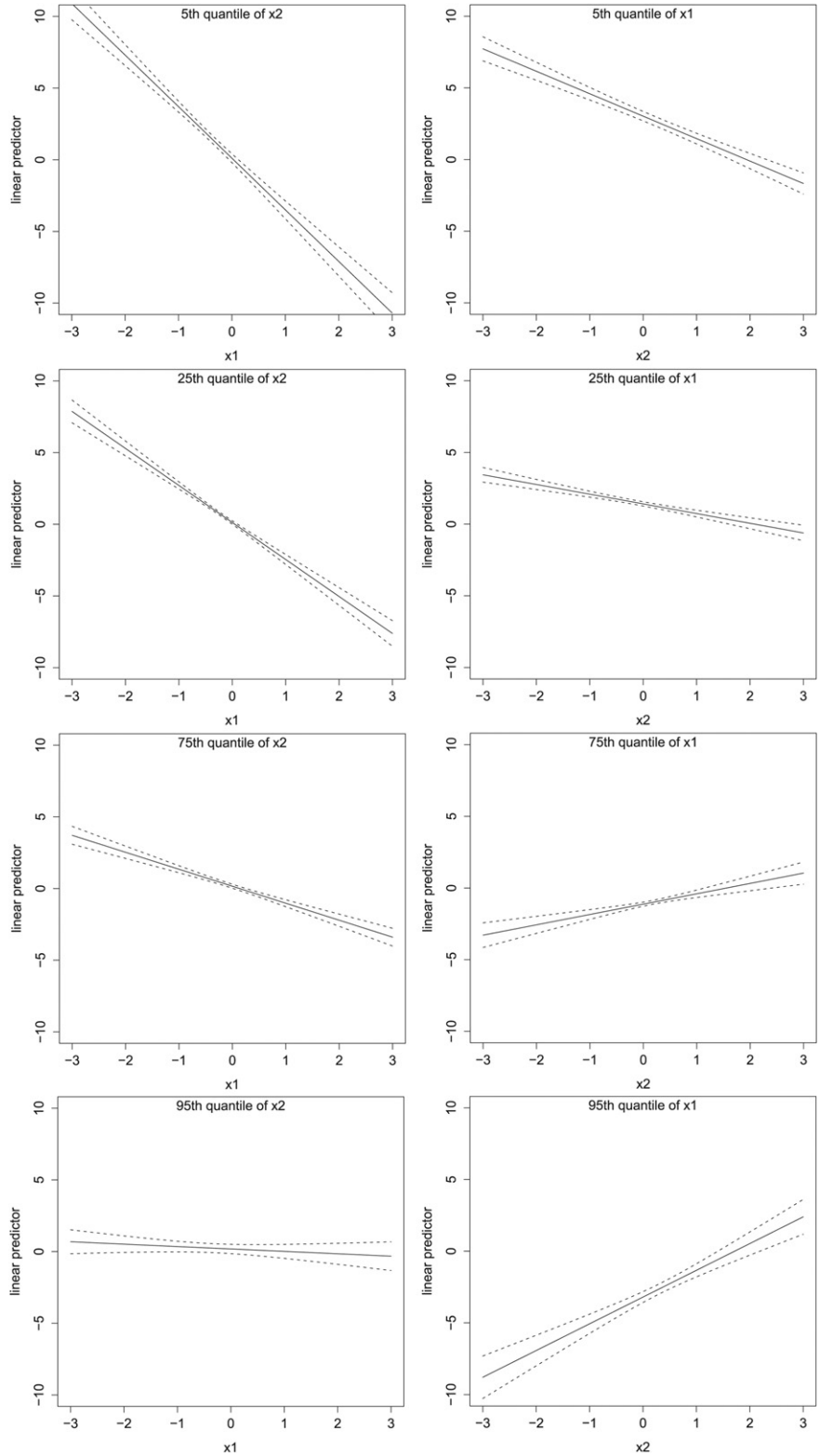

Fig. 3. Slices through the interaction surface plot for specific values. The *y*-axis shows the linear predictor of the hazard function for varying values of x_1, holding x_2 fixed at specific values (5%, 25%, 50%, 75%, and 95% quantiles; left panel) and the linear predictor of the hazard function for varying values of x_2, holding x_1 fixed at specific values (5%, 25%, 50%, 75%, and 95% quantiles; right panel).

gained at the cost of power loss. Dichotomization of data is even equal to discarding one third of the data [3]. Using cut-point models in epidemiology is in best cases just unrealistic and conservative. Considerable variability in the categories is lost and artificial steps in risk are created. In regression models where both originally continuous variables are

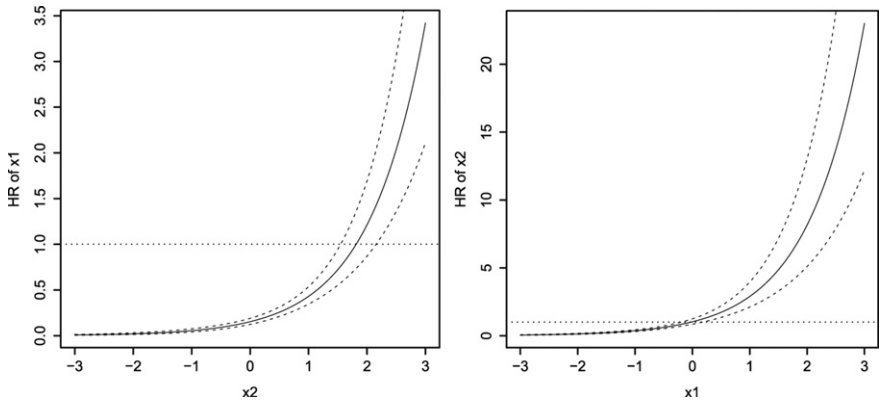

Fig. 4. Interaction plot. The *y*-axis gives the hazard ratio (HR) with point-wise 95% confidence intervals for x_1 on mortality for varying values of x_2 (on the left) and for x_2 for varying values of x_1 (on the right).

dichotomized, however, there is not only the chance for a conservative error (i.e., power loss), but the probability of false positive findings might also be increased dramatically [4]. In situations, where both explanatory variables are correlated with each other, but the partial correlation between one variable and the outcome conditioning on the other continuous variable is close to zero, dichotomization leads to bias: the effect of this variable, which would not be associated in a regression model including both variables continuously, is then overestimated. Spurious significant interaction can also occur in such a situation. An additional nonlinear effect in one of the explanatory variables creates the illusion of interaction after dichotomization.

The extent of bias worsens the higher the continuous variables are correlated. In epidemiological studies, there is hardly a situation, where two explanatory variables in one model are not correlated with each other. These findings are also true for categorizations with more than two groups [14] or if only one of the continuous variables is categorized. This was shown for building categorized age groups [15], an often-observed analysis in epidemiological studies. The more groups are chosen for categorization, however, the less bias is likely to occur.

As there are graphical methods available for interpretation purposes (see Figs. 1–4) categorization of continuous data is not necessary, anyway [16]. Another reason for categorizations might be to detect nonlinear effects. To check for nonlinearity, however, many groups are needed. Nevertheless, the real underlying structure can be missed. Therefore, flexible smoothing techniques should be preferred for this purpose. Linear and logistic regression models can be generalized to generalized additive models incorporating smooth functions in the R-package ''mgcv'' [17]. For interaction effects, tensor products of smooth functions can be constructed [18] leading to interaction surfaces reflecting the nonlinear relationship. For survival models, this technique is, to our knowledge, not implemented in common statistics programs. However, this can be done using Bayesian adaptive regression in the program BayesX [19], approximating the surface by a tensor product of Bayesian P-Splines [20]. These methods, however, are statistically more complex and this may limit their widespread use in clinical epidemiology. There is also the problem of overinterpretation and uncertainties introduced by model instabilities. In conclusion, if the linearity assumption holds, the highest statistical efficacy can be reached by modeling interaction terms continuously.

4.2. *Understanding and interpreting interaction effects*

As already stated, regression models including multiplicative interaction terms cannot be interpreted usefully just by looking at the typical output table as in Table 1. Mean centering of the variables has been proposed to make this interpretation easier. This does not alleviate the problem that the effect estimate and *P*-value only refers to one specific value of the other interacting variable, which is the mean value in that case. Mean centering has also been said to reduce the multicollinearity problem in interaction models. However, centering is just an algebraic transformation and alters nothing important, not even multicollinearity issues [12,21]. It does result in different coefficients and standard errors, but the only difference is the following: Not centering means: β_1 is the effect of x_1, when x_2 is zero. Centering means: β_1 is the effect of x_1, when x_2 is at its mean. The latter does also not help with the interpretation of interaction effects. In our example, the conditional effect for x_2 was simulated to be 0 and estimated as ~0.02. This is the effect for x_1 equal to 0. As this is also the mean of x_1, this is equal to the conditional effect after mean centering. However, Fig. 4 and the output of our proposed functions reveal that the effect of x_2 is significantly different from 0 for 98.1% of the observed data. In conclusion, presenting such a table as Table 1 at all is not very useful for interpretation purposes, no matter if centering was performed or not. One needs methods spanning the complete range of values for proper interpretation of effects on variables, which are involved in interaction effects.

For this purpose, we propose different graphical visualization methods, which can be used for GLMs or Cox

models. The twisted plane in Fig. 1 shows how the effects of both interacting variables change with changing values of the other respective variable. However, there is a danger of overinterpretation at the tails of the distributions. Effects that can only be seen for very rare high or low values might be overrated. By cutting out slices out of this twisted plane for specific values (Fig. 3) together with its confidence bands, one can see, if the interaction is only triggered by a small percentage of the data at the tails of the distribution or if it affects most of the observations. Conditional effects with their corresponding *P*-values or confidence intervals can also be given out for a specified range of values (function ''getRegion'' or ''getRegionCox,'' see Fig. 4). The interaction plots exemplified in Fig. 4 are sufficient to show the effects for the complete range of both constituting variables together with their point-wise confidence intervals. Reporting the significance region and the percentage of the observations falling into this region can help to better judge the possible implications: Are the ranges of variables where the interaction applies realistic and relevant? An interaction effect might not be interesting especially for clinical interpretation, if it is only driven by a small percentage of observations.

5. Conclusion

As the interpretation of interaction effects between the two continuous variables is not straightforward, continuous variables are categorized in most clinical epidemiological publications leading to a loss of power and information. We give an overview over common misconceptions in the interpretation of interaction effects and propose several graphical visualization methods to ease this interpretation. Together with the calculation of significance regions, these plots can give researchers and clinicians the information needed to better assess the clinical relevance and implications of interaction effects.

Appendix

Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jclinepi.2012.02.013.

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