Evaluating and presenting complex interactions in clinical research

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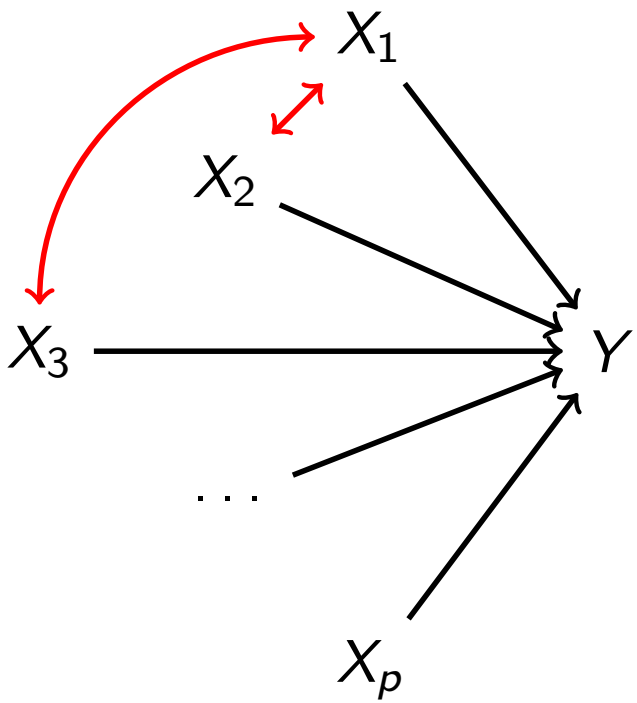
Outline

1. Interaction analysis in clinical and public health research
2. Estimating interaction in time-to-event analysis
3. Flexible estimation of additive interaction from the Cox model
4. Summary and discussion

General definition of interaction

In the broadest sense, we talk about interaction analysis when we want to evaluate the joint contribution of 2 or more factors as they relate to an outcome of interest.



Interaction in clinical and public health research

Some examples of joint contributions of interest in clinical and public health:

- The effect of a given treatment, or risk factor, is heterogeneous over patients' characteristics [effect modification]
  e.g. sex stratification
- The simultaneous presence of both factors further enhances the outcome activation [biological or clinical interaction / synergy and antagonism]
  e.g. unhealthy diet + smoking and the risk of stroke
- Two factors operate in a sequential way [mediation + interaction] / not discussed today
  e.g. unhealthy diet, BMI, and the risk of stroke

Interaction from a statistical model

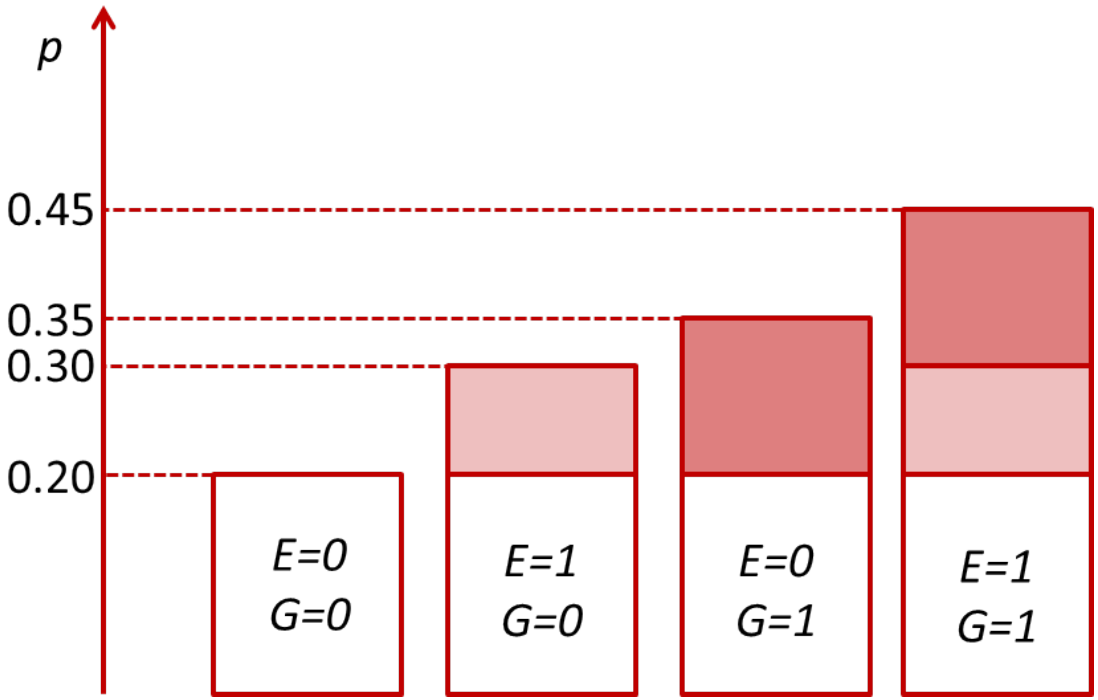
Given 2 variables G and E, we assess their interaction (or effect modification) in predicting Y, by including a product term $E \cdot G$ in the statistical model

$$f(Y) = \beta_0 + \beta_1 \cdot E + \beta_2 \cdot G + \beta_3 \cdot E \cdot G$$

- β_1 and β_2 are the main effects of E and G
- β_3 describes the additional change in $f(Y)$ when both E and G are present
- $\beta_3 = 0$ implies absence of interaction; $\beta_3 > 0$ positive interaction; $\beta_3 < 0$ negative interaction
- The p-value associated with the test $\beta_3 = 0$ can be used as p-value for interaction

Additive vs multiplicative interaction (example with 2 binary covariates)

Is the combined effect larger than the sum of the 2 main effects?

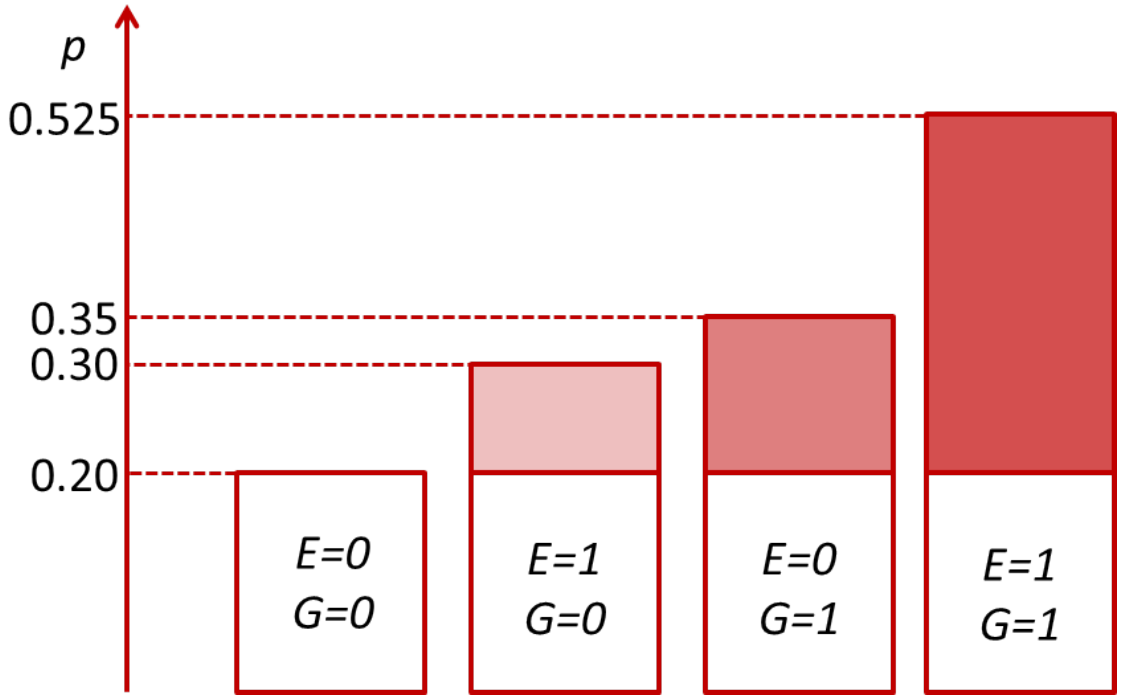


Absence of additive interaction

$$p_{11} = p_{10} + p_{01} - p_{00}$$

$$0.35 + 0.30 - 0.20 = 0.45$$

Is the combined effect larger than the product of the 2 main effects?



Absence of multiplicative interaction

$$p_{11} = (p_{10} \times p_{01})/p_{00}$$

$$(0.35 \times 0.30)/0.20 = 0.525$$

- It is common to have some level of interaction in at least one scale
- Whether one is interested on a scale or the other will depend on biological / clinical assessment
- Additive interaction is a relevant public health measure (VanderWeele & Knol 2014). It informs, for example, on group-specific treatments effects
- Evaluating and presenting interaction according to both scales has been widely recommended (VanderWeele 2015)

- What interaction is tested in a statistical model depends on the model scale
- A statistical model on the linear scale can be used to evaluate statistical interaction on the additive scale

$$P(Y = 1|G = g, E = e) = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 ge$$

- A statistical model on the log-linear scale can be used to evaluate statistical interaction on the multiplicative scale

$$\log[P(Y = 1|G = g, E = e)] = \beta_0 + \beta_1 g + \beta_2 e + \beta_3 ge$$

Interaction in survival analysis

- Cox regression, the most common statistical approach for time-to-event data, is a log-linear model
- Inclusion of a product-term in a Cox regression model allows evaluating departures from multiplicative effects

Cox regression

$$h(t; g, e) = h_0(t)e^{\beta_1 g + \beta_2 e + \beta_3 ge}$$

- e^{β_3} gives a measure of multiplicative interaction for hazard ratios (HR)
- Presenting both risks and hazard rates is recommended
- Current approaches for additive interaction on the additive scale in survival analysis are based on alternative modeling techniques (Rod et al. 2012, Bellavia et al. 2016) and do not focus on the absolute risk dimension

Additive interaction from a Cox model

- There is a mathematical relationship between hazard and absolute risk
- HRs from a Cox model can be translated to absolute risk differences (ARDs) of the event at a given time point t
- Extension of this derivation to interactions on the ARDs scale have been scarce, and are not available for increasingly complex modeling scenarios

	Multiplicative		Additive	
	Estimate and display	CI / test	Estimate and display	CI / test
2 binary and/or categorical covariates	Available	Available	Available	Available
1 binary and 1 continuous	Available	Available	Focus of this presentation	Focus of this presentation
1 binary and 1 continuous, with splines	Previous work from our groups	Previous work from our groups	Focus of this presentation	Focus of this presentation

Binary predictors case

- Explicit formulas to derive ARDs from Cox models have only been derived for models without interactions and binary predictors (Ozenne et al. 2017)
- By applying mathematical relationships, individual survival probabilities (corresponding to 1-risk) at t can instead be predicted to provide the same result
- Prediction options are available in most software (e.g. `baseline` statement in SAS proc PHREG, `predict` and `predictSurvProb` in `R`)

- In the simple case of a single binary predictor (e.g. assigned treatments) the following 2 approaches provide the same estimate of the model-based approach:
  - Average predicted survival/risk over the 2 groups
  - Fit a OLS regression model with predicted survival as dep variable and the group of interest
- We have confirmed this result under several simulation scenarios (varying underlying distributions and censoring mechanisms)
- Here a simple example in R:

Cox model with a single binary predictor (trt2)

```
fit1<-coxph(Surv(days2miistr, miistrfu) ~ trt2,
data=data, ties="breslow",y=TRUE,x=TRUE)
```

Direct estimation of absolute risk difference (riskRegression package)

```
riskreg <- ate(fit1, data = data, treatment = "trt2", times = 1096.75)
as.numeric(summary(riskreg)$diffRisk$estimate)
[1] 0.02158322
```

Predict survival probabilities

```
data$surv<- 1- predictSurvProb(fit1,newdata=data,time=1096.75)
```

Average risk over levels of trt2

```
risk0<-mean(data$surv[data$trt2==0])
risk1<-mean(data$surv[data$trt2==1])
arr<-risk1-risk0
arr
[1] 0.02158322
```

OLS model with predicted survival as a function of trt2

```
a<-lm(surv~trt2,data=data)
round(summary(a)$coefficients,5)[2,1]
[1] 0.02158
```

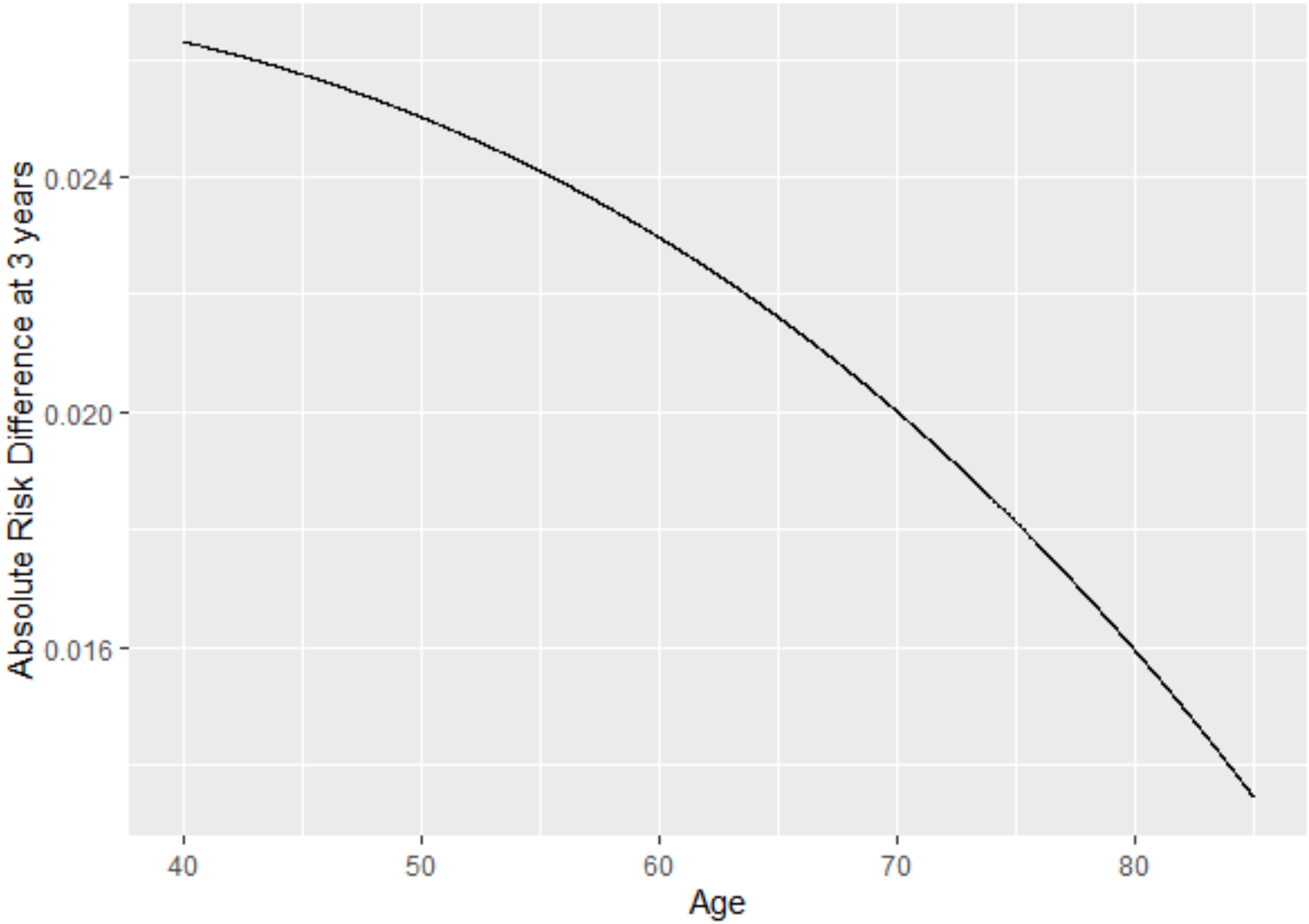
Additive interaction with a continuous predictor

Individual prediction can be obtained for any model, so the latter approaches can be extended to more complex models.

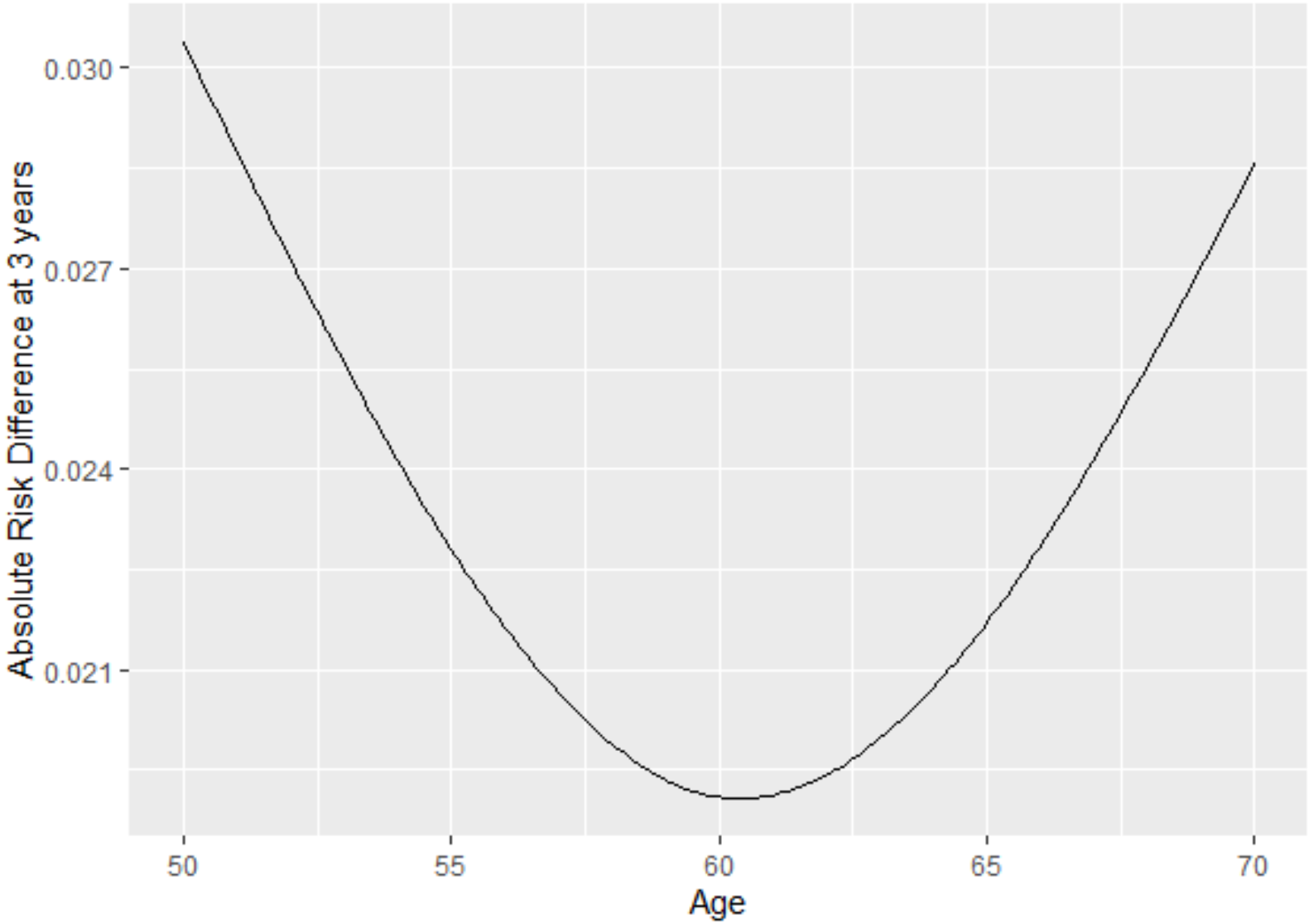
Here is a Cox model with treatment (binary), age (continuous), and their interaction, where we compute the "average" predicted risk over a finer grid of potential values (i.e. all combinations of trt2 and AGE)

```
fit_int1 <- coxph(Surv(days2miistr, miistrfu) ~ trt2*AGE,
data=data, ties="breslow",y=TRUE,x=TRUE)

newdat = expand.grid(AGE = seq(20,80, by = .1),
trt2 = unique(data$trt2) )

newdat$surv<- 1- predictSurvProb(fit1,newdata=newdat,time=1096.75)
```

By including an interaction, the ARD between the 2 levels of treatment will vary over levels of AGE

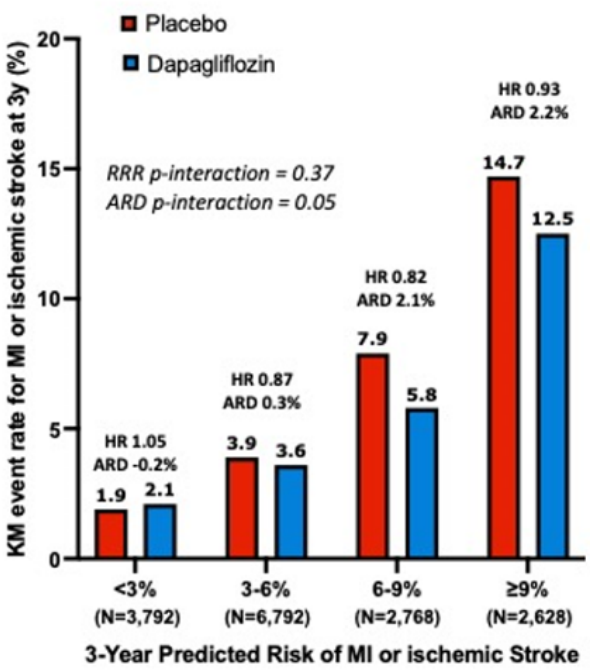


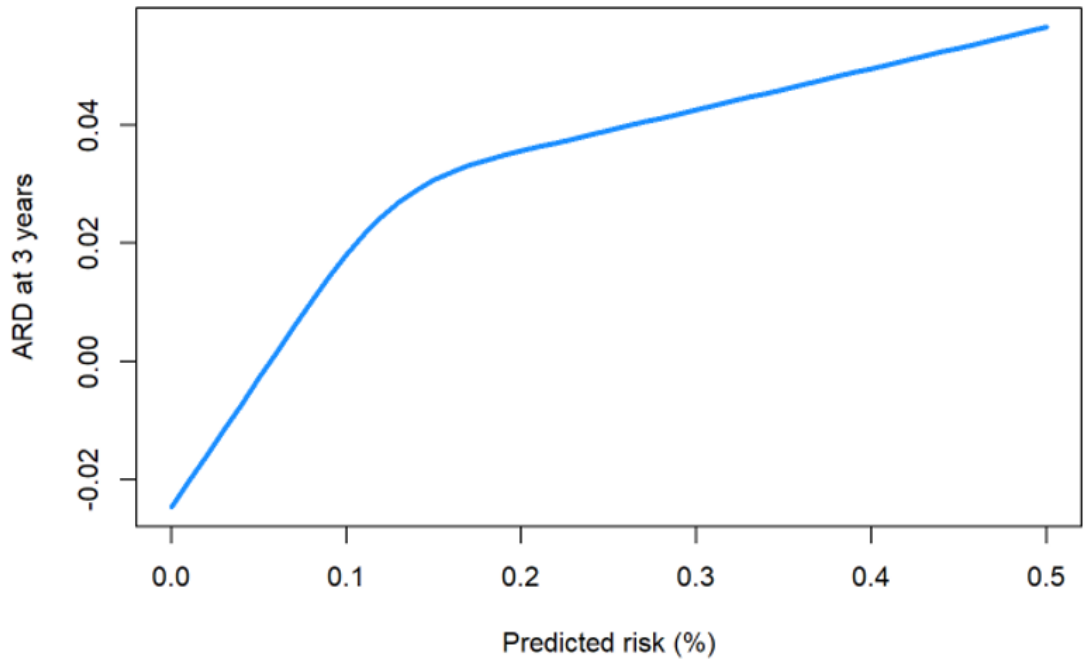
This approach can be extended to incorporate additional flexibility (e.g. restricted cubic splines)



Illustrative example

We replicated results from a recent study on treatment interaction for a newly developed risk score for MI/ischemic stroke (Berg et al. 2022)





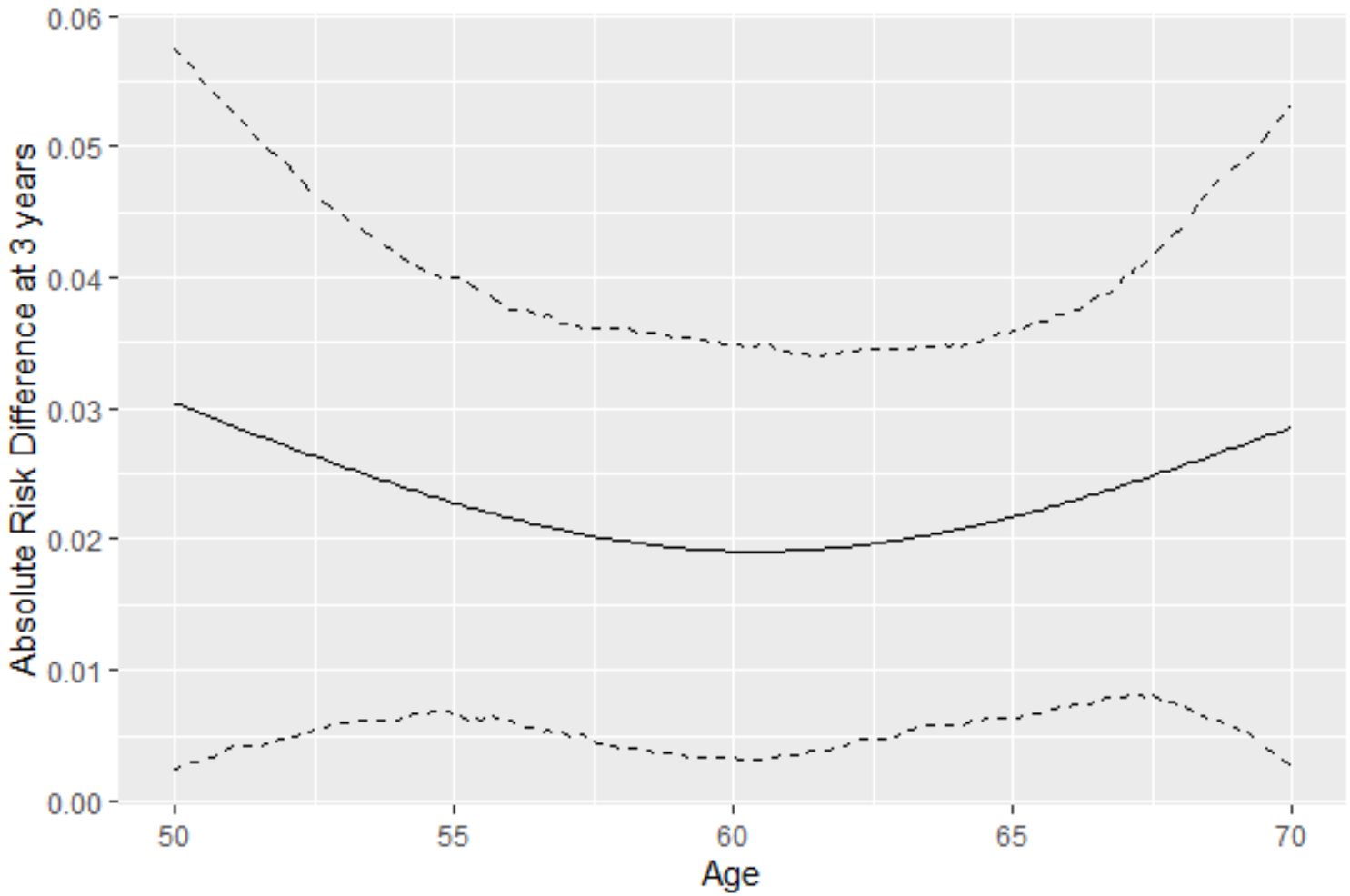
The flexible assessment of the continuous variable with splines confirms previous findings and provides additional information (e.g. plateau at higher predicted risk)

Adjusting for covariates

- Approaches based on individual prediction allow for covariates adjustment (from the original Cox model)
- The additional step requires the specification of how covariates are handled in the prediction
- Both marginal and conditional adjustment can be evaluated
  - Conditional: define covariate patterns in the prediction grid
  - Marginal: fit a marginal model (e.g. with IPW)
- For conditional adjustment, different techniques have been presented for adjusted survival curves (Ghali et al, 2001, Cole & Hernan 2004)

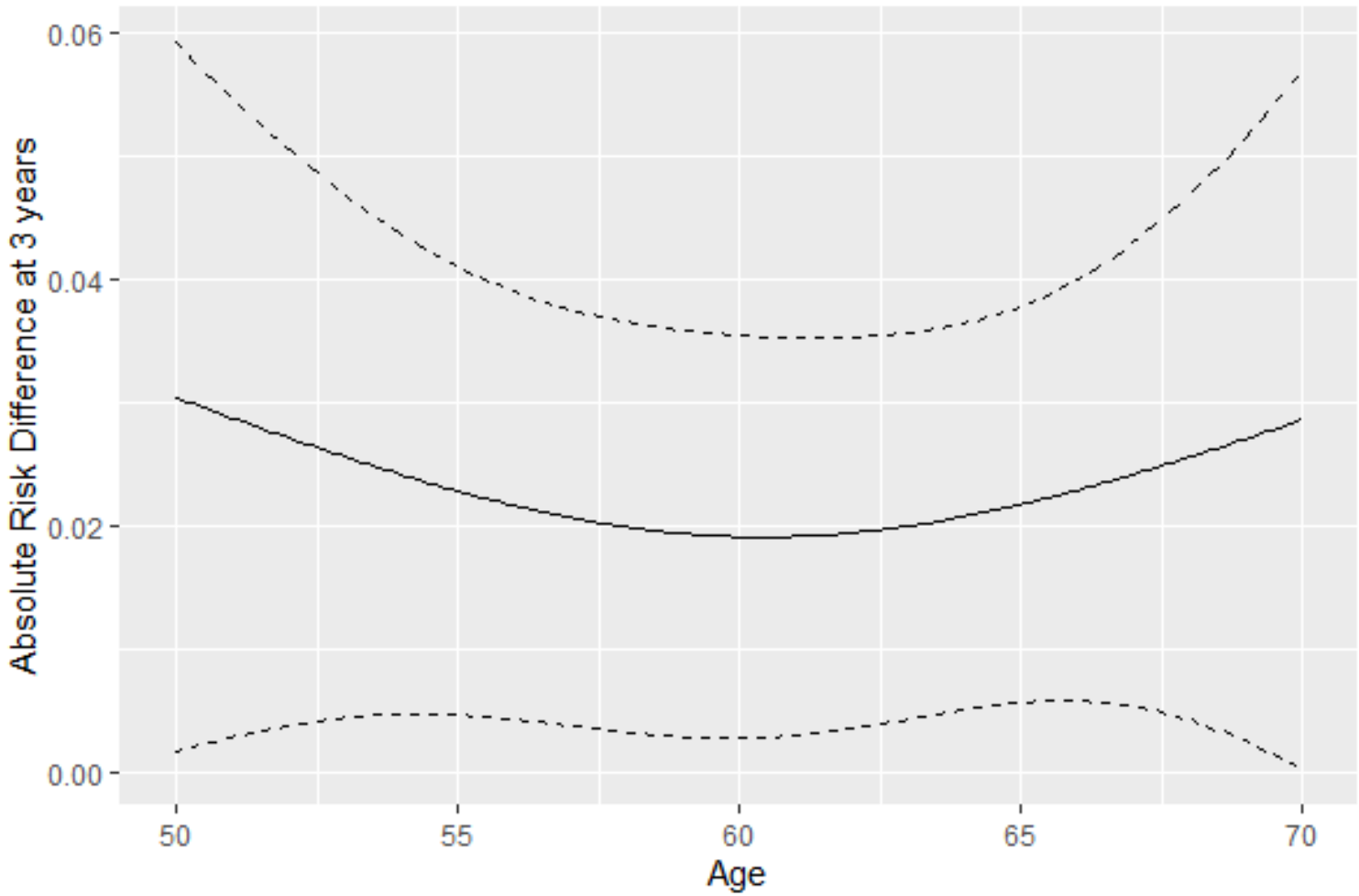
Confidence intervals/bands

We have integrated 2 approaches: providing confidence bands by incorporating individual predictions within bootstrap (1000 replications in this figure)



Alternatively, calculating CIs from the standard errors (SE) of the ARD. This is be done by estimating SEs of individual predictions over the 2 groups of the binary covariate (SE_0 and SE_1) and by deriving:

$$SE(ARD) = \sqrt{SE_0^2 + SE_1^2}$$



Test for interactions

- Researchers might want to include a test (p-value) for interaction on both scales
- Especially in this context, this procedure should be discouraged:
  - The test for the product term in the Cox model will test for interaction on the hazard scale. The potential test based on the SE of the prediction could be used as a test for additive interaction
  - With splines, however, interaction changes over levels of the second covariates. CIs from the plot are a better indicator than pvalues
  - In the previous figure, for example, one could assess the levels of age where the CI for ARD does not include 0

Software development

We are currently working on integrating the presented procedures into SAS macros and R packages:

- R: we have published the `interactionRCS` package to estimate and display flexible interactions on the hazard scale (credits to Dr. G. Melloni). ARDS scale will be integrated in the next version.
- SAS: macros will be included in upcoming publications (credits to Dr. J. Park)

QR code for interactionRCS vignette

We'll post future updates on andreabellavia.github.io or on Twitter @andreabellavia

Summary

- Interaction analysis is a critical component of clinical and public health research
- Research questions often require evaluating both additive and multiplicative scales
- With time-to-event data, tools to estimate additive interaction are scarce, especially in the presence of continuous predictors
- We have developed a comprehensive framework for the estimation and presentation of flexible interaction on the additive risk scale
- Currently finalizing user-friendly software tools

Future directions

- Assessing the interaction between 1 binary and 1 continuous covariate only touches the surface of the real-world complexities
- Future work will address settings with 2 continuous covariates, both with potential non-linear effects
- How to extend interaction analysis on the additive risks scale with higher-dimensional interactions (more than 2 variables) has not been discussed
- Machine learning techniques that allow assessing interactions usually provide clinically meaningless measures based on the multiplicative scale (e.g. H-statistics from gradient boosting)

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