

# Detecting an interaction between treatment and a continuous covariate: a comparison between two approaches

**Willi Sauerbrei**

**IMBI, University Medical Center Freiburg**

**Patrick Royston**

**MRC Clinical Trials Unit, London**

# Overview

- **Continuous predictive factors**
  - **STEPP**
  - **MFPI**
- **Example**
- **Stability**
- **Conclusions**

# Detecting predictive factors

- **Most popular approach**
  - Treatment effect in separate subgroups
  - Has several problems (Assman et al 2000)
- **Test of treatment/covariate interaction required**
  - For `binary` covariate standard test for interaction available
- **Continuous covariate**
  - Often categorized into two groups

# Categorizing a continuous covariate

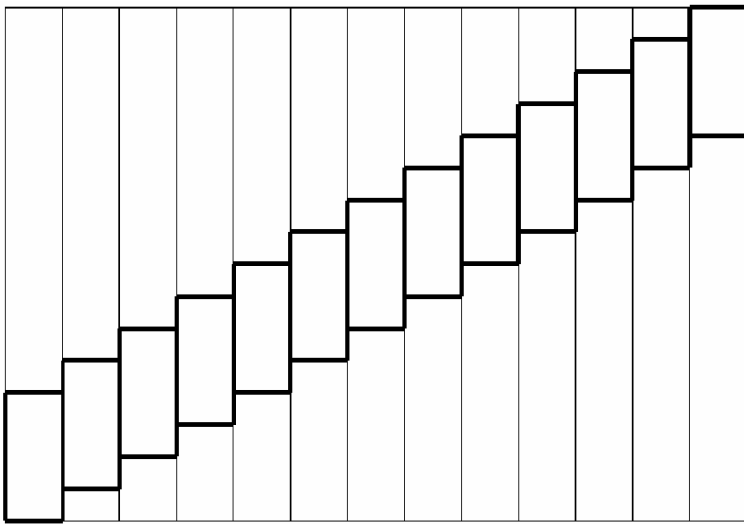
- **How many cutpoints?**
- **Position of the cutpoint(s)**
- **Loss of information  $\Rightarrow$  loss of power**

# New approaches for continuous covariates

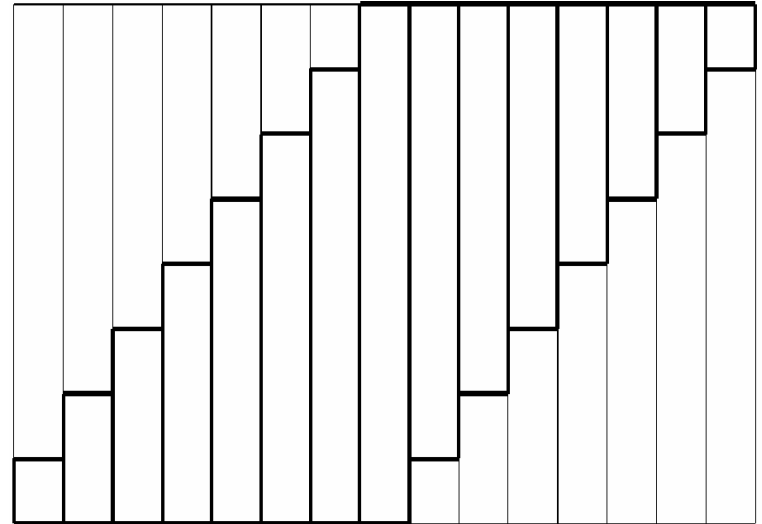
- **STEPP**  
**Subpopulation treatment effect pattern plots**  
**Bonetti & Gelber 2000**
- **MFPI**  
**Multivariable fractional polynomial**  
**interaction approach**  
**Royston & Sauerbrei 2004**

# STEPP

## Sequences of overlapping subpopulations



**Sliding window**



**Tail oriented**

# STEPP

## Estimates in subpopulations

$$\sqrt{n} \begin{bmatrix} \hat{\theta}_1 - \theta_1 \\ \vdots \\ \hat{\theta}_K - \theta_K \end{bmatrix} \xrightarrow{d} N_K \left[ \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, \Sigma \right]$$

$\hat{\theta}_1, \dots, \hat{\theta}_k$  treatment effect in  
subpopulation  $P_1, \dots, P_k$

# STEPP

**Overlapping populations, therefore  
correlation between  $\hat{\theta}_1, \dots, \hat{\theta}_k$**

**Simultaneous confidence band and tests  
proposed**

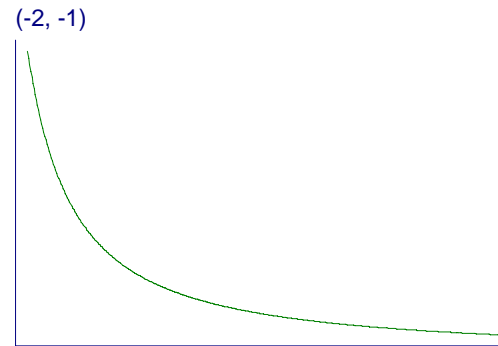
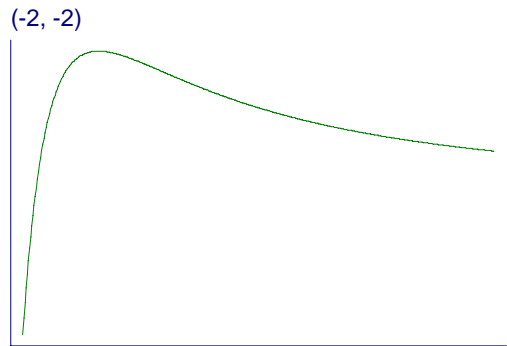
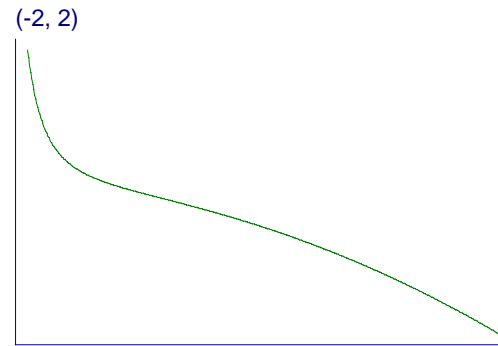
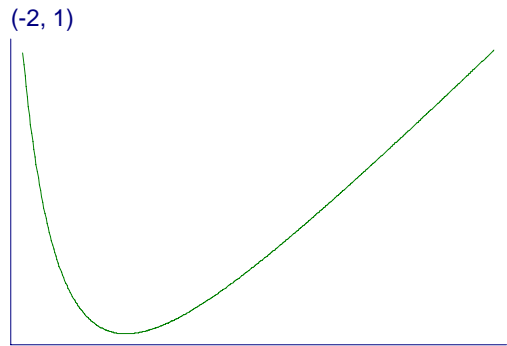
# Fractional polynomial models

- ***Fractional*** polynomial of degree 2 with powers  $\mathbf{p} = (p_1, p_2)$  is defined as

$$FP2 = \beta_1 X^{p_1} + \beta_2 X^{p_2}$$

- Powers  $\mathbf{p}$  are taken from a predefined set  $S = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$

# Some examples of fractional polynomial curves



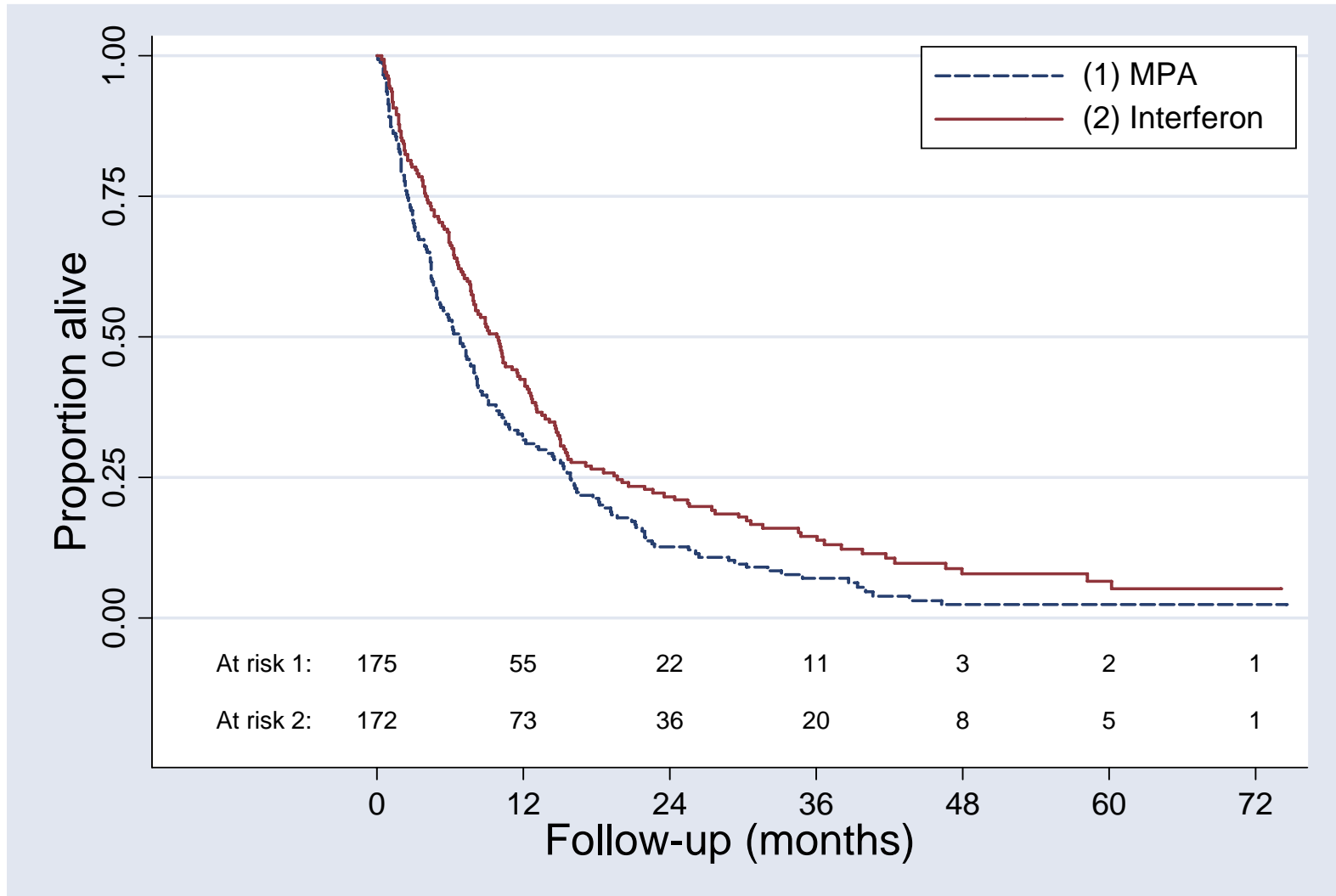
# MFPI

- **Have one continuous factor  $X$  of interest**
- **Use other prognostic factors to build an adjustment model, e.g. by MFP**
- **MFP – combine backward elimination with search for best FP function**
- **Find best FP2 transformation of  $X$  with same powers in each treatment group**
- **LRT of equality of reg coefficients**
- **Test against main effects model(no interaction) based on  $\chi^2$  with 2df**
- **Distinguish predefined hypothesis - hypothesis searching**

# RCT: Metastatic renal carcinoma

Comparison of MPA with interferon

N = 347, 322 Death



**Overall: Interferon is better ( $p < 0.01$ )**

- **Is the treatment effect similar in all patients?**

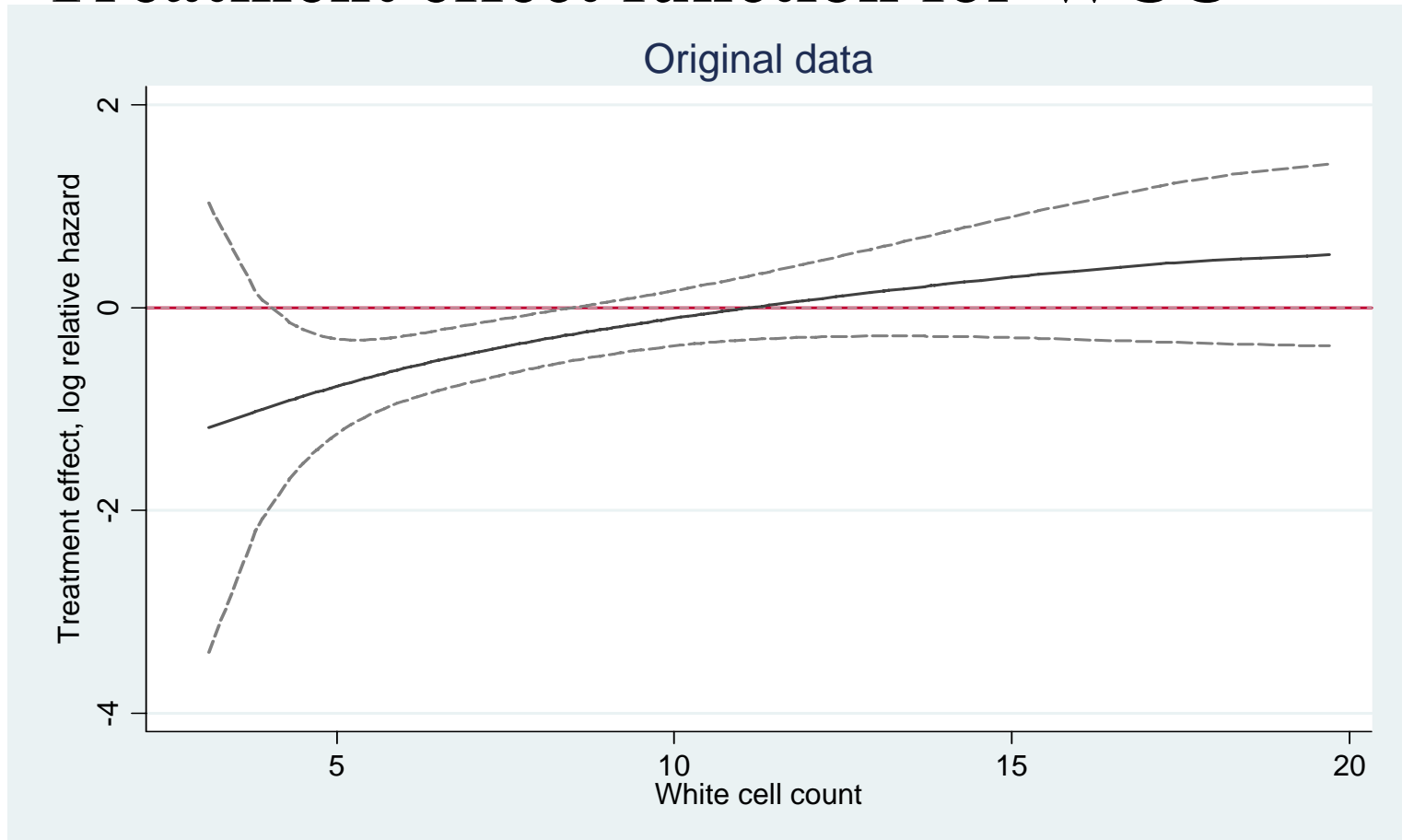
**Sensible questions?**

- **Yes, from our point of view**

- **Ten factors available for the investigation of treatment – covariate interactions**

# MFPI

## Treatment effect function for WCC



**Only a result of complex (mis-)modelling?**

# MFPI

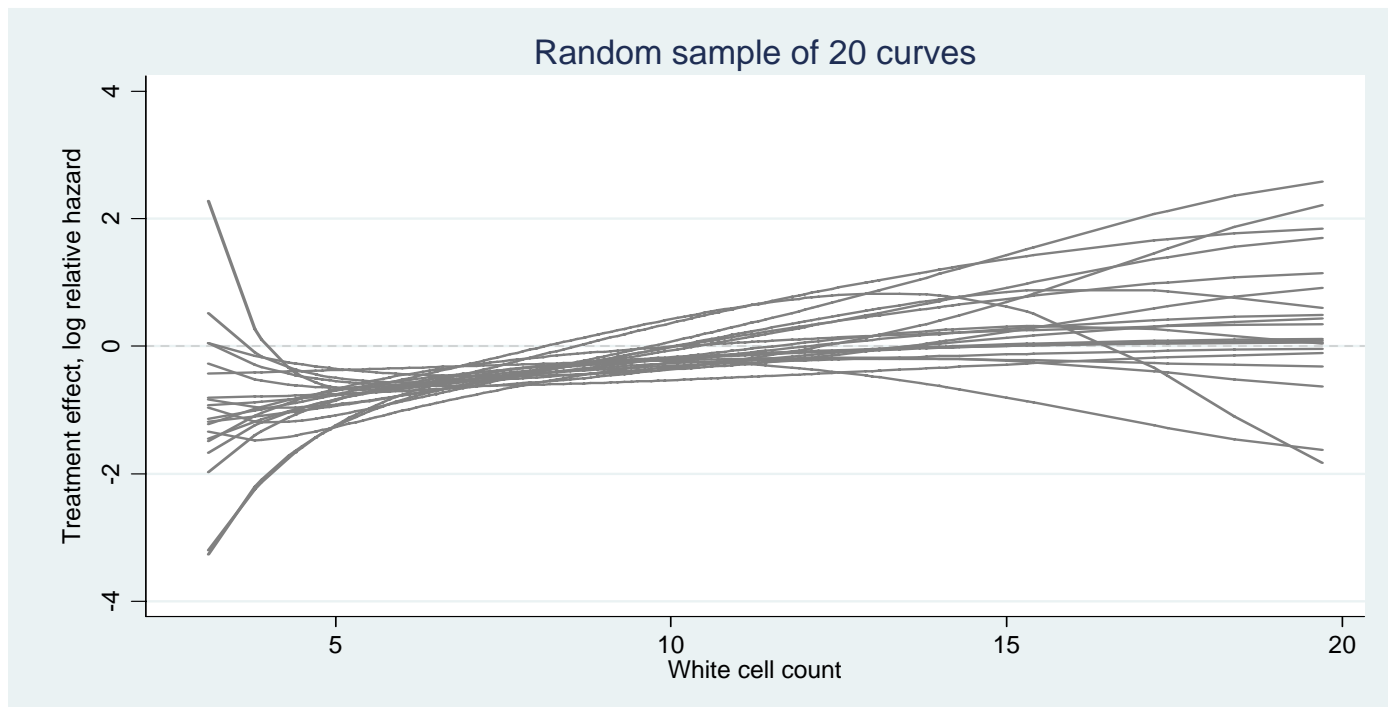
## Stability investigation of the treatment effect function for WCC

**100 bootstrap replications of the MFPI procedure**

**In each replication:**

**1.Step: Select adjustment model**

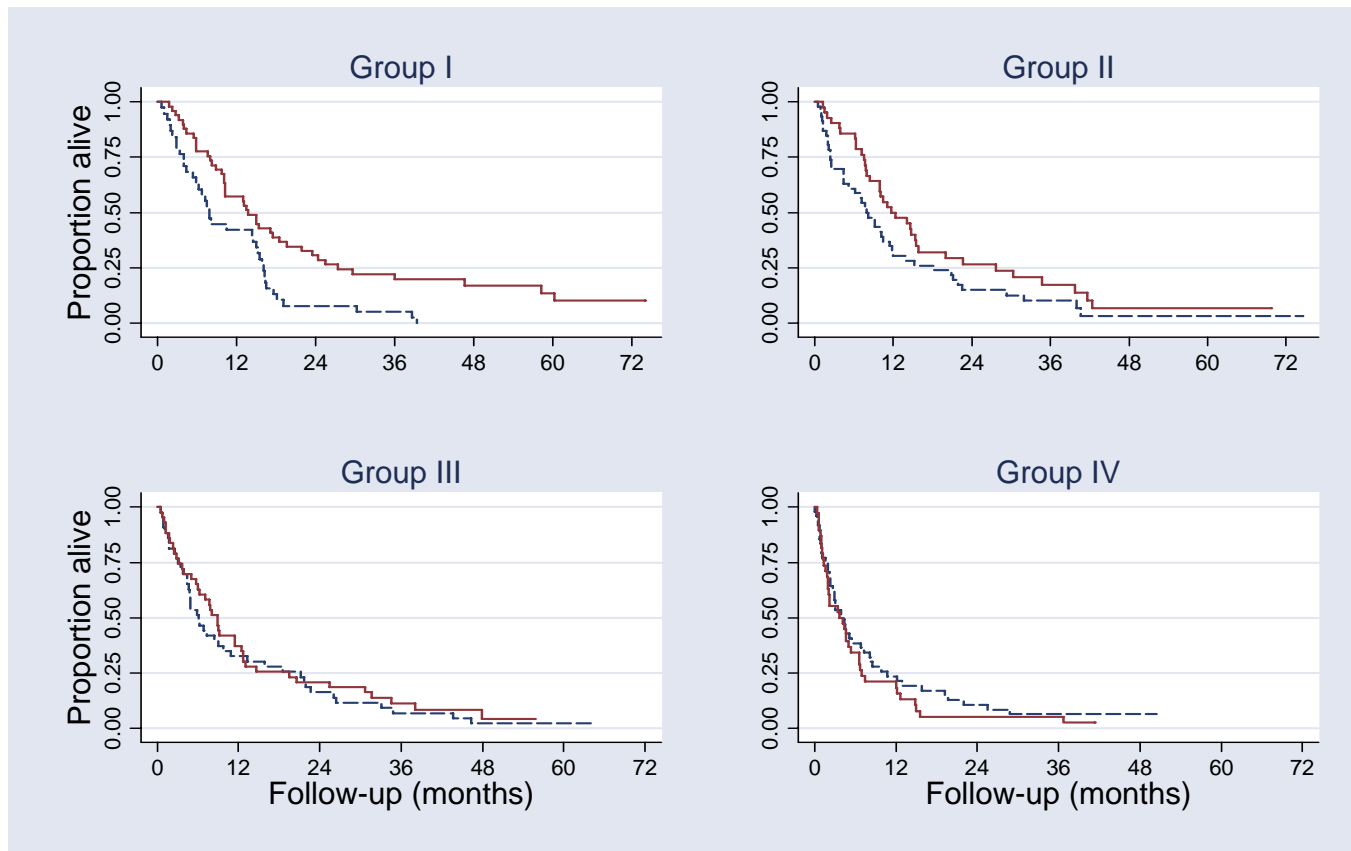
**2.Step: Estimate treatment effect function**



# Does the MFPI model agree with the data?

Check proposed trend

Treatment effect in subgroups defined by WCC



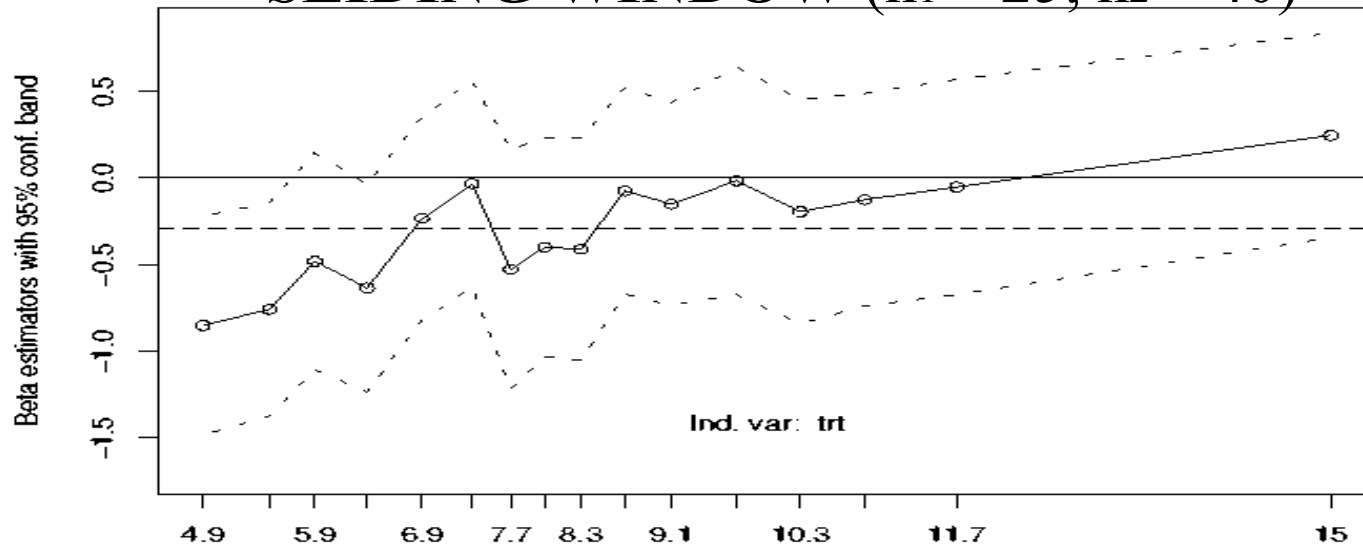
HR (Interferon to MPA; adjusted values similar) **overall: 0.75 (0.60 – 0.93)**

**I : 0.53 (0.34 – 0.83)      II : 0.69 (0.44 – 1.07)**

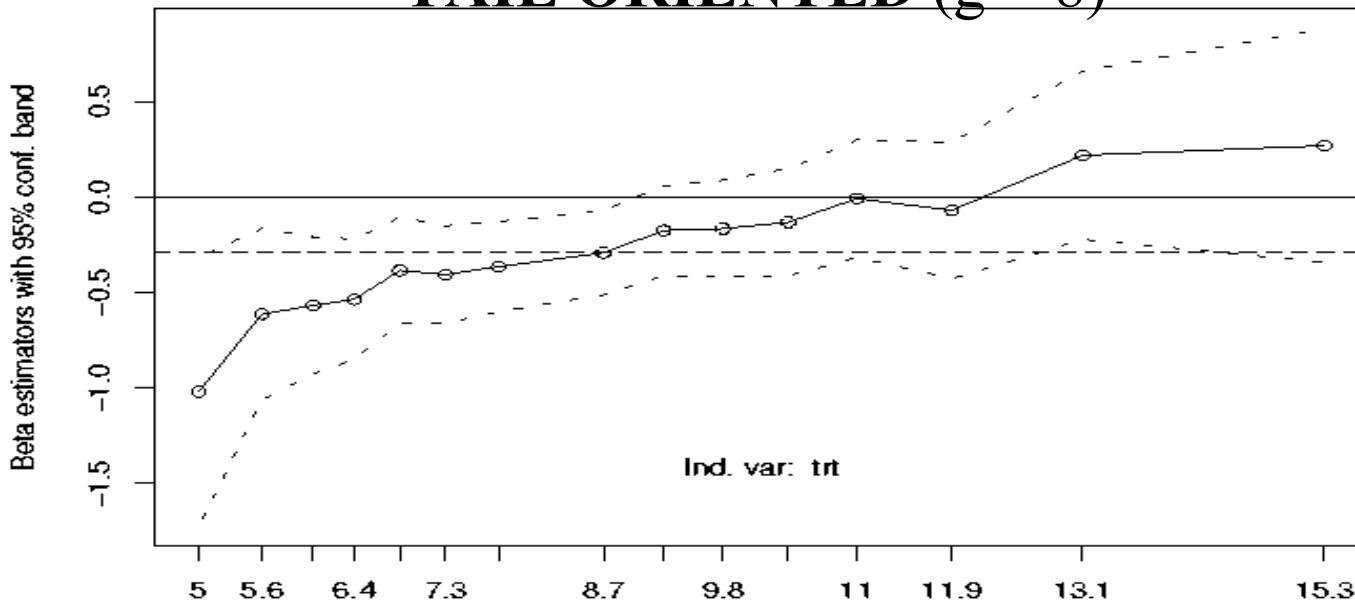
**III : 0.89 (0.57 – 1.37)      IV : 1.32 (0.85 – 2.05)**

# STEPP – Interaction with WCC

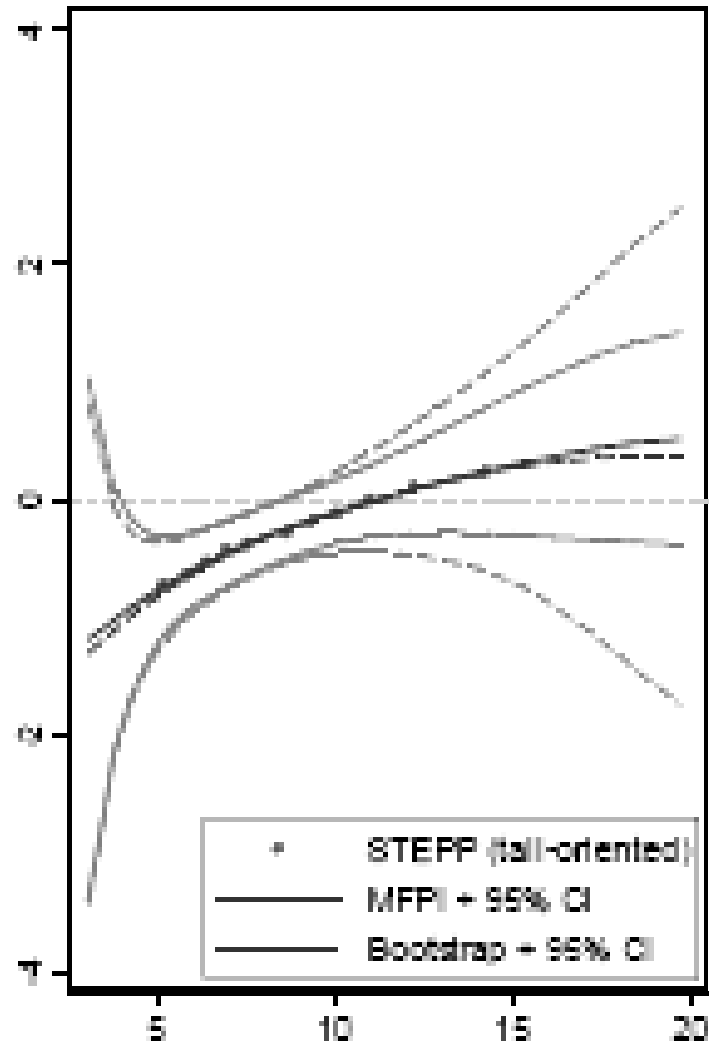
**SLIDING WINDOW** ( $n_1 = 25, n_2 = 40$ )



**TAIL ORIENTED** ( $g = 8$ )



# STEPP as check of MFPI

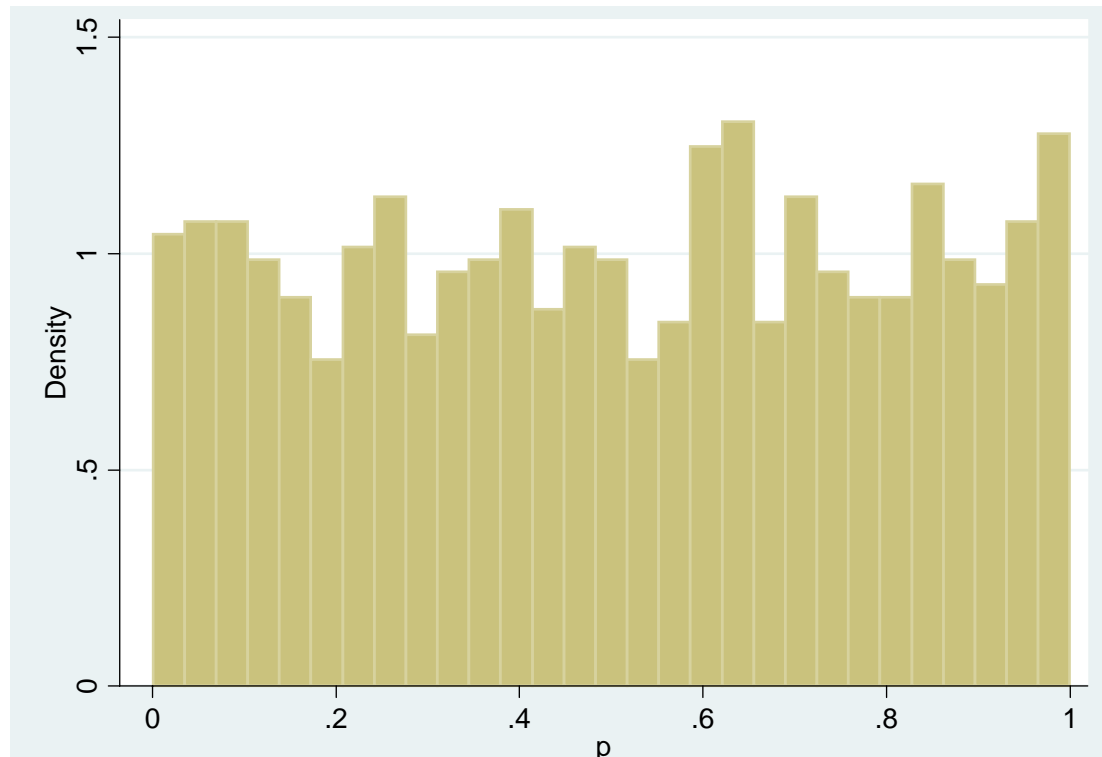


# MFPI – Type I error

**Random permutation of a continuous covariate  
(haemoglobin)**

→ **no interaction**

**Distribution of P-value from test of interaction  
1000 runs, Type I error: 0.054**



# Conclusions

- **Cutpoints** approaches have **several problems**
- **More power** by using all information **from continuous factors**
- **STEPP** and **MFPI** may detect important predictive effects which may be missed by standard methodology
- **STEPP**: step in the right direction, still depends on cutpoints and is more unstable
- **MFPI**: no cutpoints required, estimates continuous treatment effect function, promising results from stability and type I error investigations
- Important **differentiation**:  
**prespecified hypothesis** or **hypothesis generation**  
(interpretation, multiple testing)

# References

**Assman SF, Pocock S, Enos LE, Kasten LE (2000): Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet, 355, 1064-1069.**

**Bonetti M, Gelber RD (2000): A graphical method to assess treatment-covariate interactions using the Cox model on subsets of the data. Statistics in Medicine, 19, 2595-2609.**

**Bonetti M, Gelber RD (2004): Patterns of treatment effects in subsets of patients in clinical trials. Biostatistics, 5,465-481.**

**Royston P, Sauerbrei W (2004): A new approach to modelling interactions between treatment and covariates in clinical trials by using fractional polynomials. Statistics in Medicine, 23, 2509-2525.**

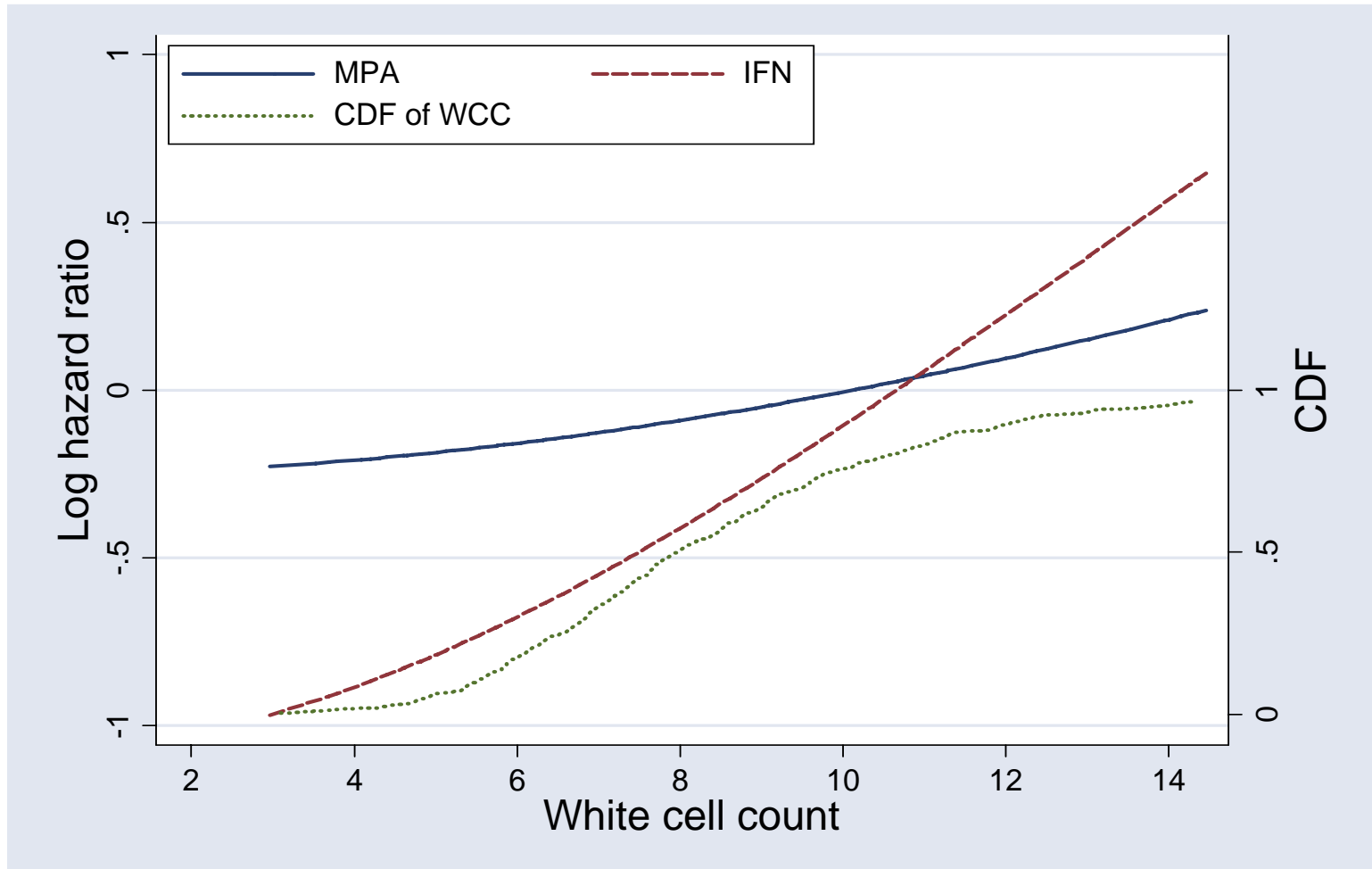
**Royston P, Sauerbrei W, Ritchie A (2004): Is treatment with interferon- $\alpha$  effective in all patients with metastatic renal carcinoma? A new approach to the investigation of interactions. British Journal of Cancer, 90, 794-799.**

**Sauerbrei W, Royston P (1999): Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. Journal of the Royal Statistical Society A, 162, 71-94.**

**Sauerbrei W, Royston P, Zapien K (2006): Detecting an interaction between treatment and a continuous covariate: a comparison between two approaches, submitted.**

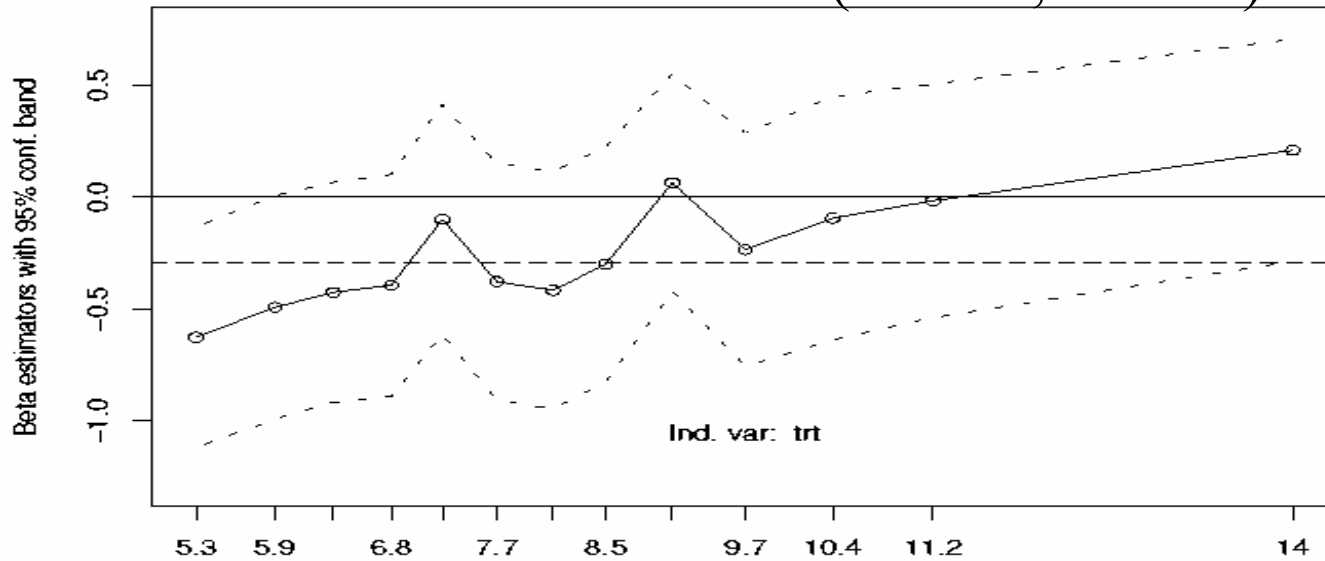
# MFPI

Effect of WCC is best modelled with an FP2 (2, 3).

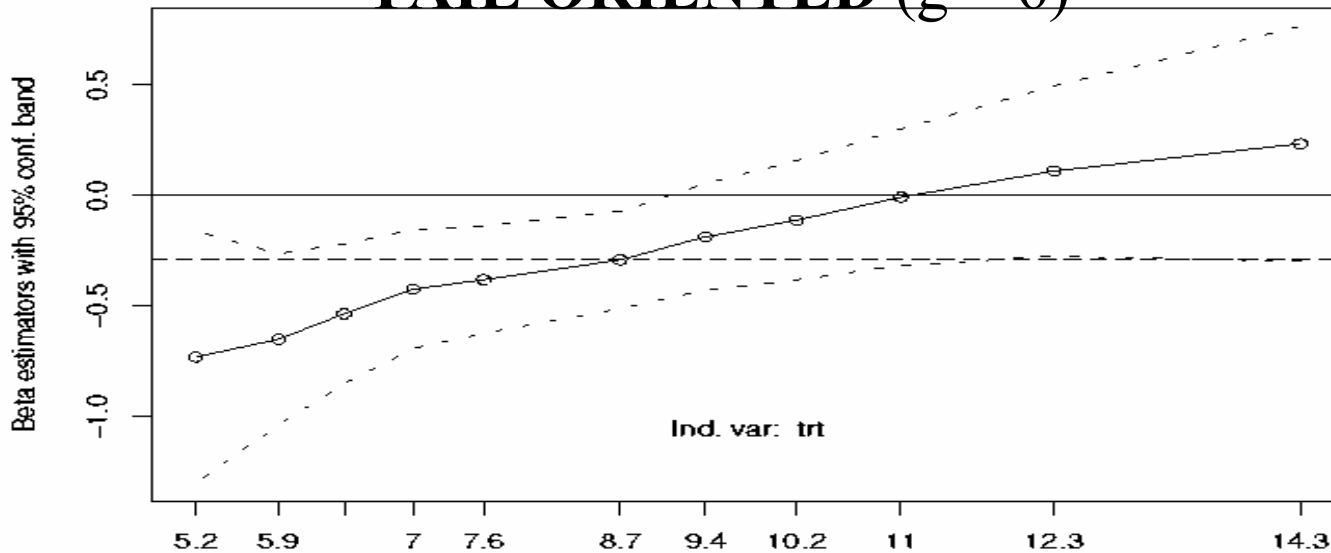


# STEPP – Interaction with WCC

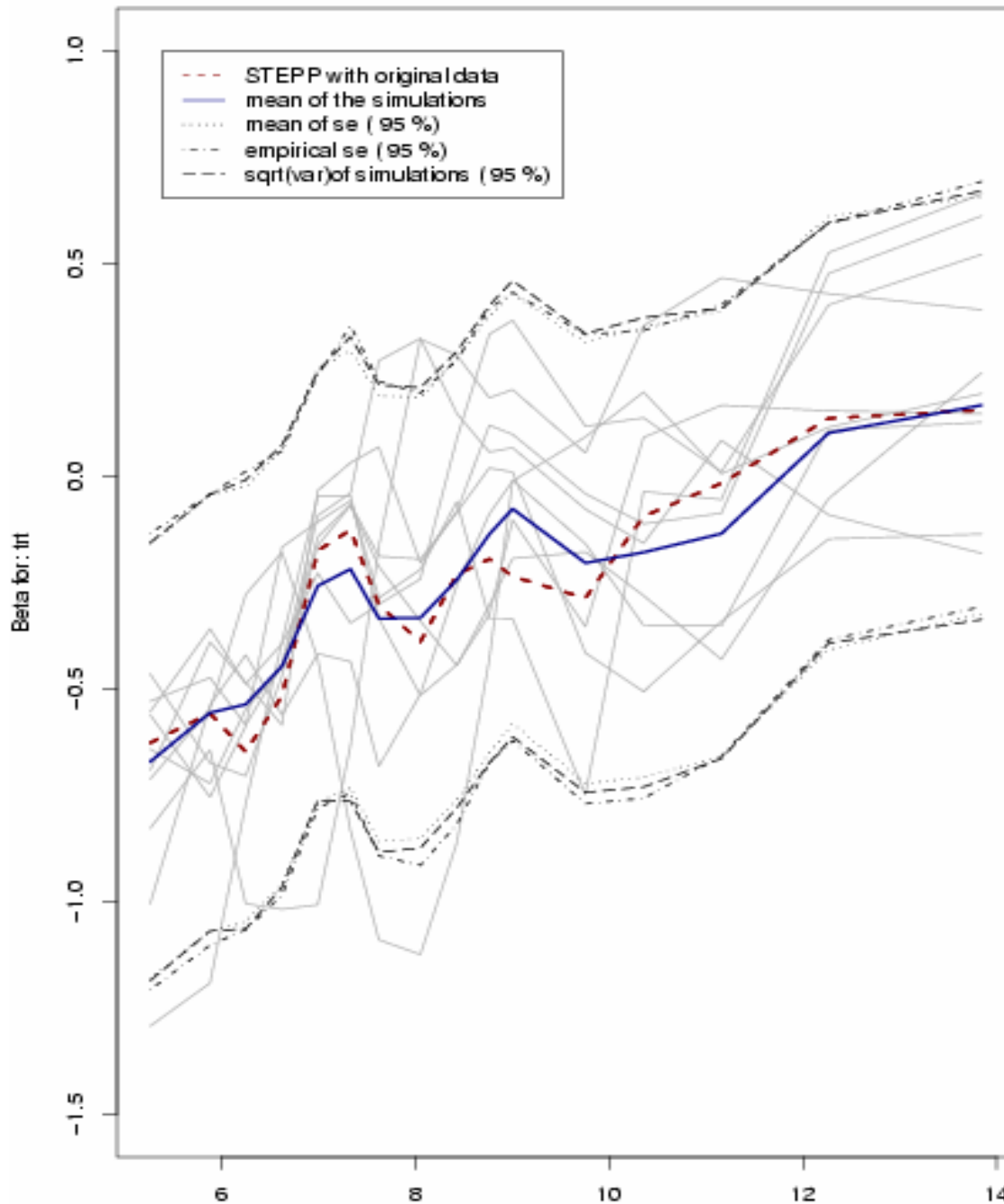
## SLIDING WINDOW ( $n_1 = 40, n_2 = 60$ )



## TAIL ORIENTED ( $g = 6$ )



# STEPP – Interaction with WCC

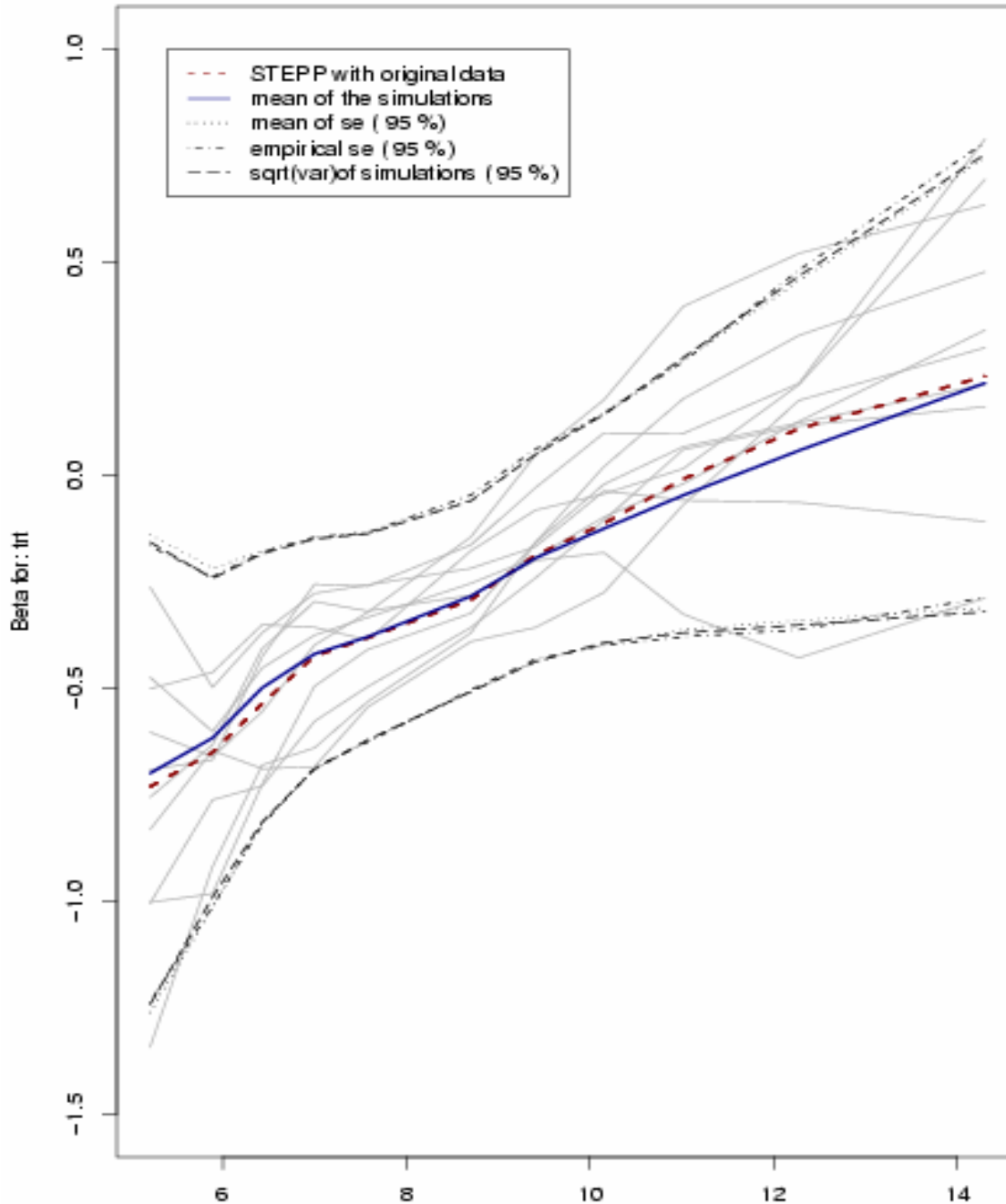


**1000 Bootstrap  
replications**

**SLIDING WINDOW**

$(n_1 = 40, n_2 = 60)$

# STEPP – Interaction with WCC



**1000 Bootstrap  
replications**

**TAIL ORIENTED**

**(g = 6)**