A non-technical overview of the proportional hazards assumption in survival analysis

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http://pauldickman.com/talk/

Overview of today's talk

Please interrupt!

- About me.
- Recap of $S(t)$ and $h(t)$ and how they are related.
- What is the PH assumption [emphasising similarity with other modelling assumptions].
- Examples/illustrations, including how to report studies with non-PH.
- ~~Assessing the PH assumption.~~ [only covered briefly]
- ~~Technical details of fitting non-PH models.~~
- Example in Stata [Time permitting]
- Slides at: `https://pauldickman.com/talk/`

About me

- Born in Sydney Australia;
  studied mathematics and statistics in Newcastle (Australia).
- Worked in health services research;
  dabbled in industrial process control and quality improvement.
- Arrived in Sweden November 1993 for a 10 month visit to cancer epidemiology unit at KI. Stayed in Sweden for most of my PhD.
- Short Postdoc periods at Finnish Cancer Registry
  and Karolinska Institutet (cancer epidemiology).
- Joined current department in March 1999, attracted by the strong research environment and possibilities in register-based epidemiology.

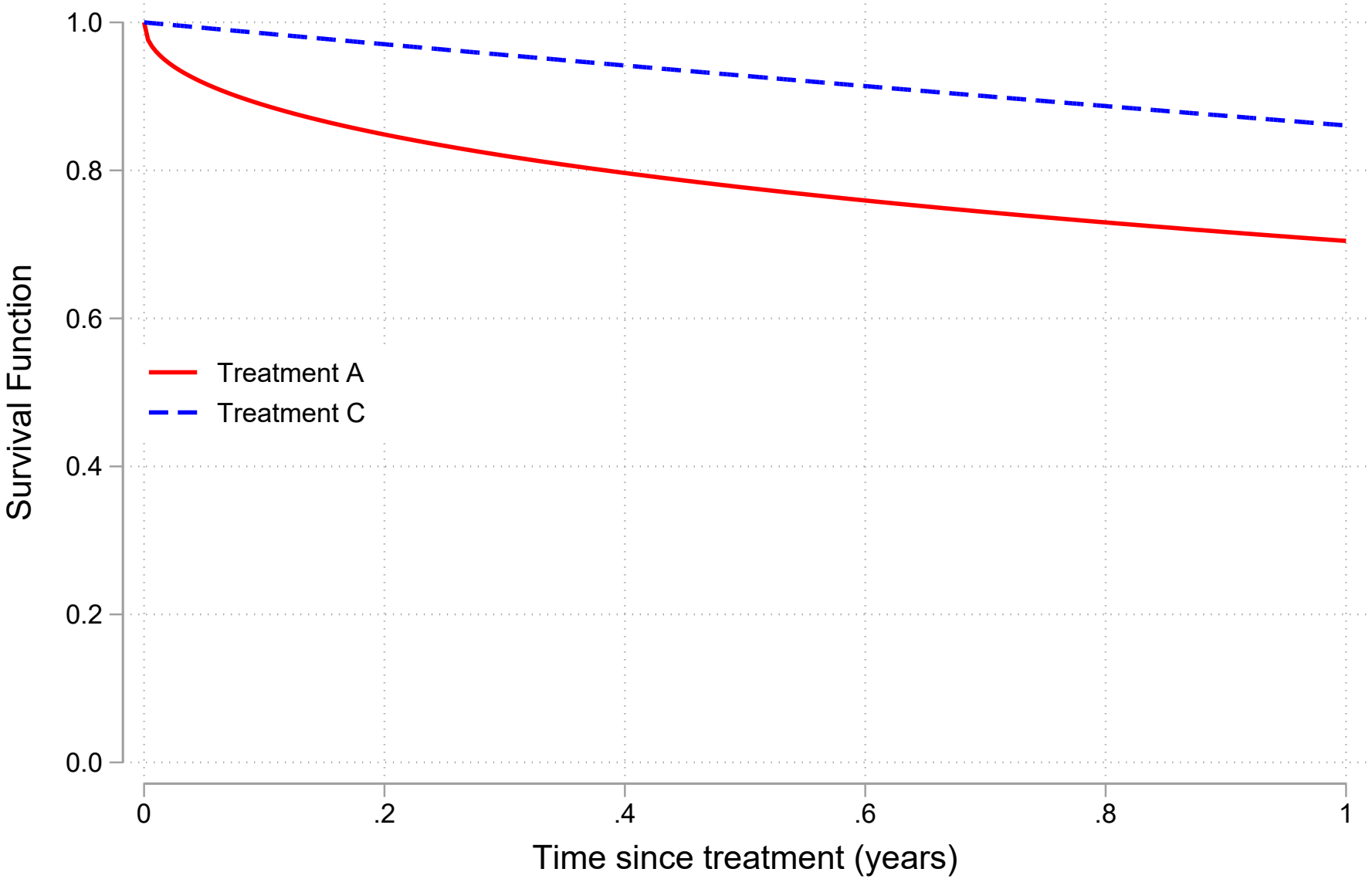
My research interests

- Development and application of methods for population-based cancer survival analysis, particularly the estimation and modeling of net survival.
- General interest in statistical aspects of the design, analysis, and reporting of epidemiological studies.
- Epidemiology, with particular focus on cancer epidemiology and perinatal/reproductive epidemiology.
- Lots of administrative work.

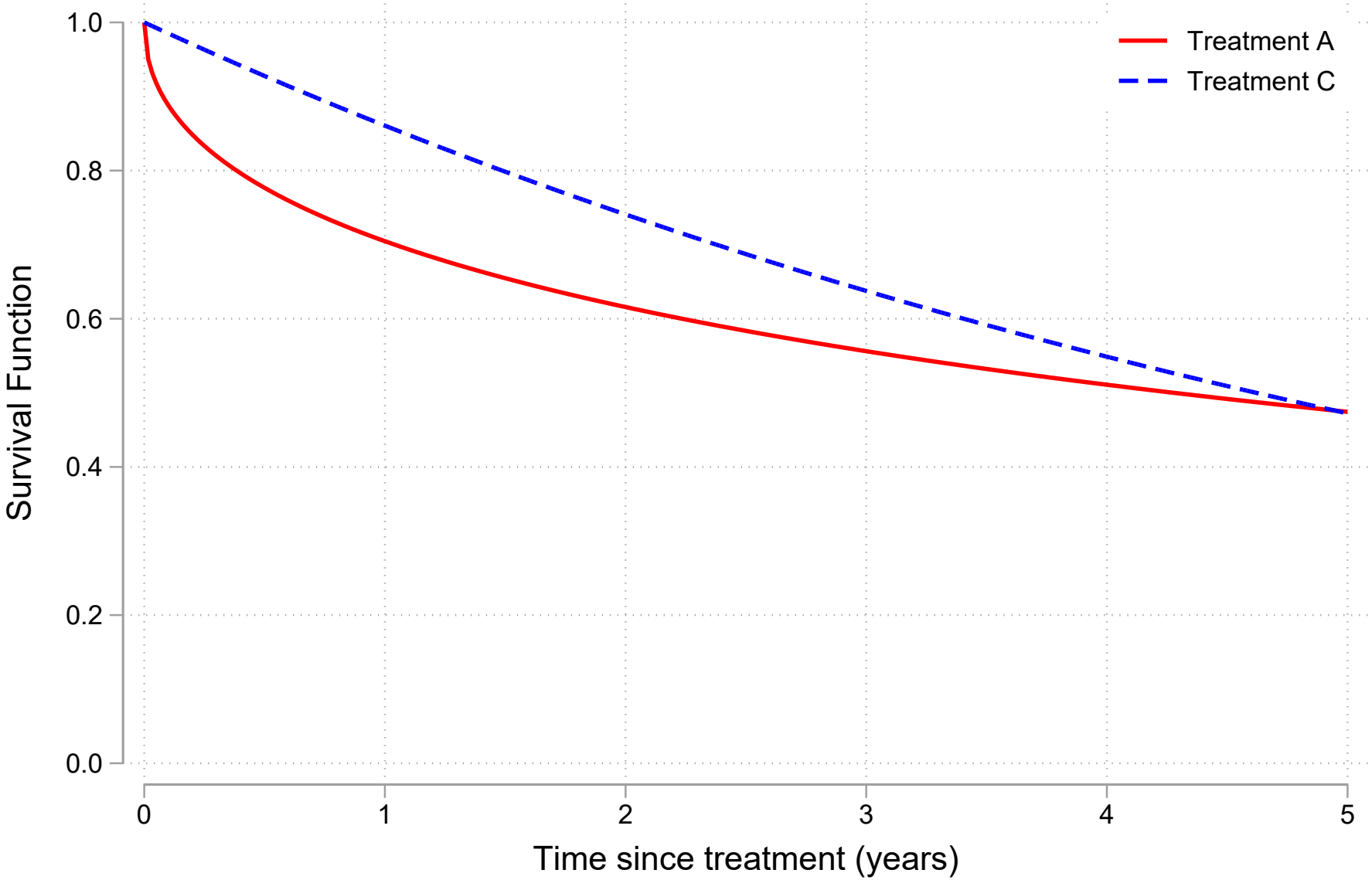
Recap: The survivor function $S(t)$ and the hazard function $h(t)$

- In survival analysis we can express the outcome in terms of either the survival proportion (the proportion who do not experience the event) or the event rate (hazard).
- I am assuming you are familiar with the basic concepts of the survivor function, $S(t)$, and the hazard function, $h(t)$.
- I will nevertheless, take some time to give a brief recap while also introducing the concept of proportional hazards (which I assume many of you have previously met).
- I have included some mathematical detail for completeness, but won't go through it during the seminar.

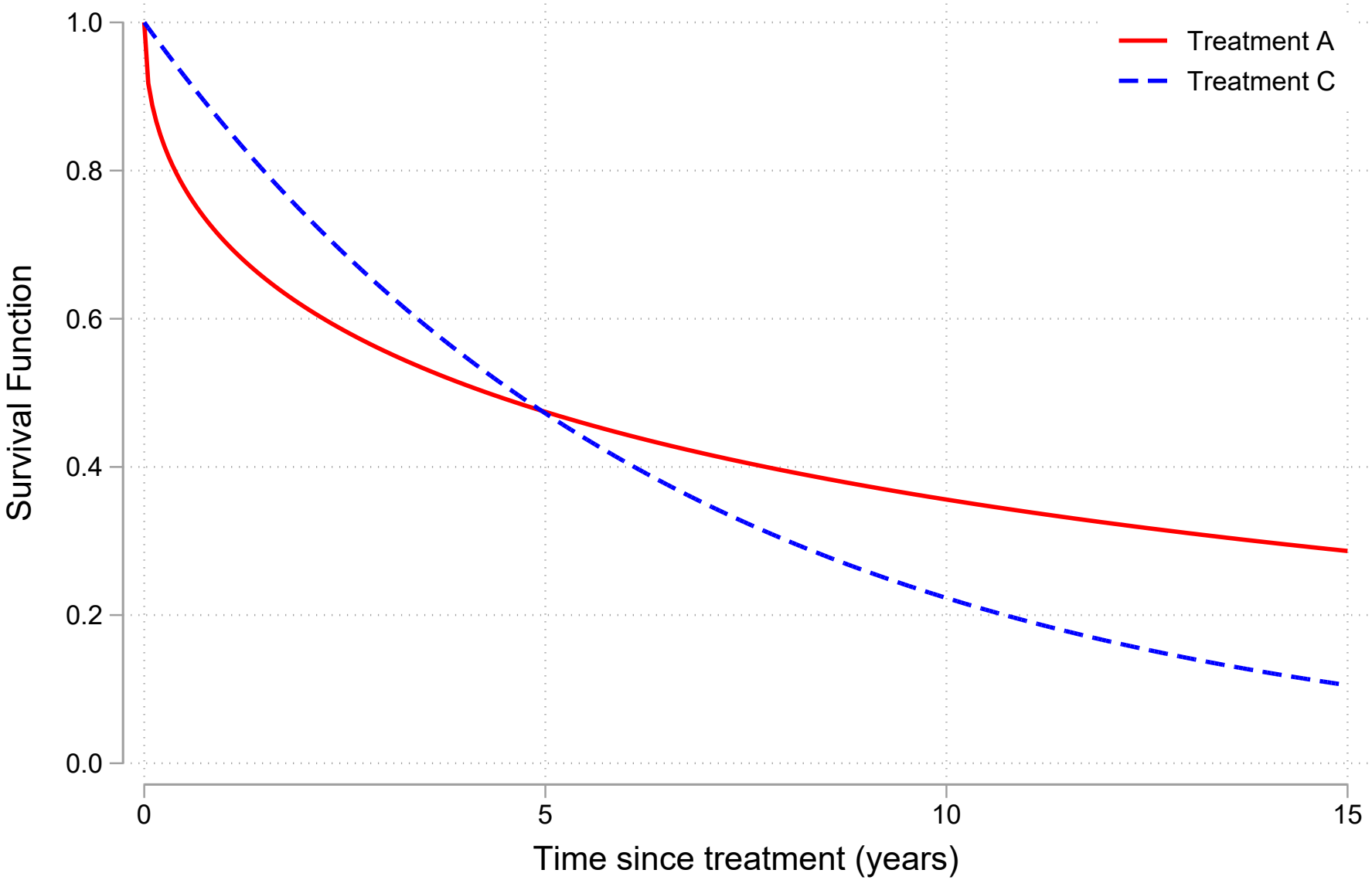
Which treatment (A or C) has the best survival?



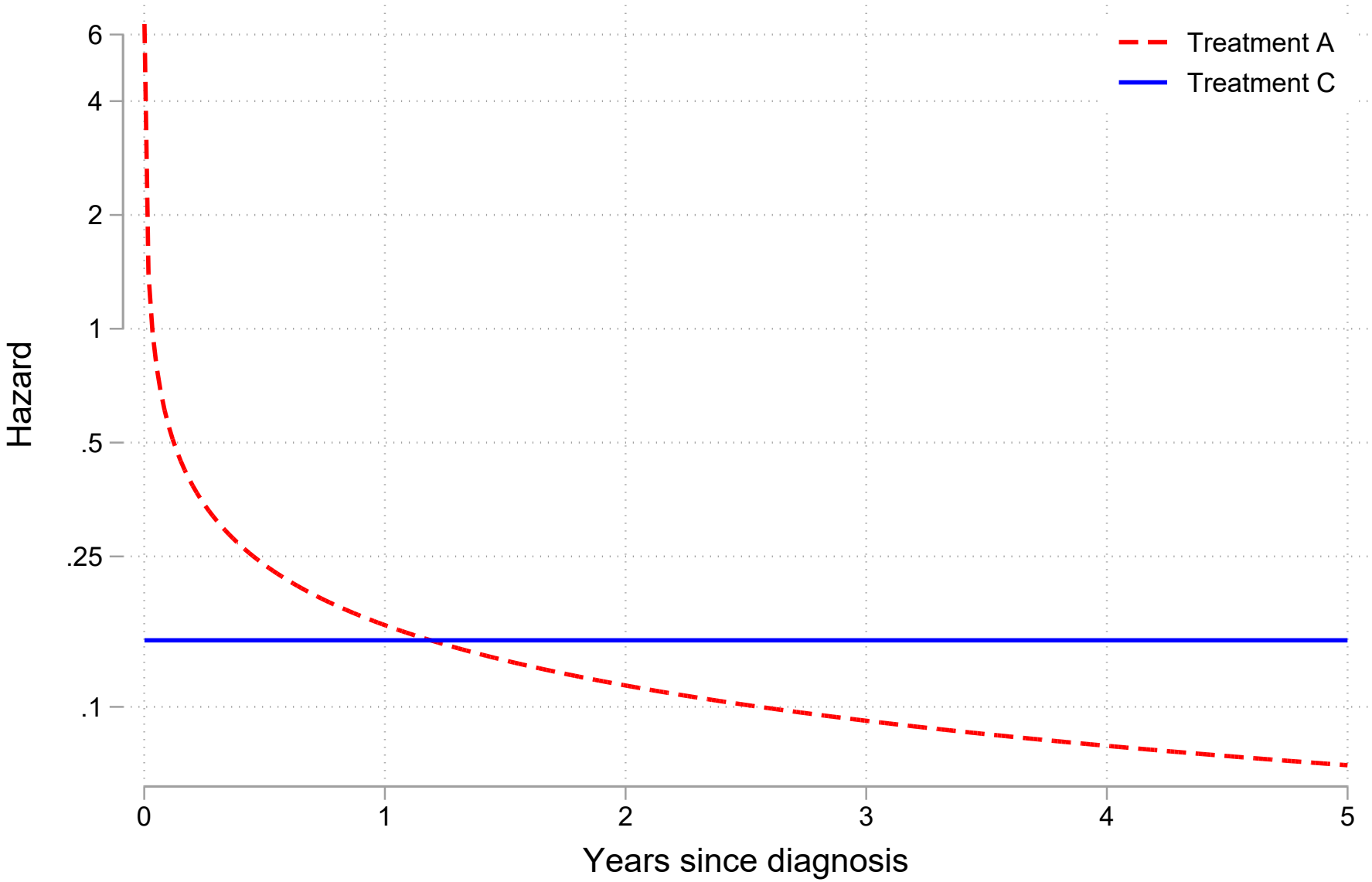
Which treatment (A or C) has the best survival?



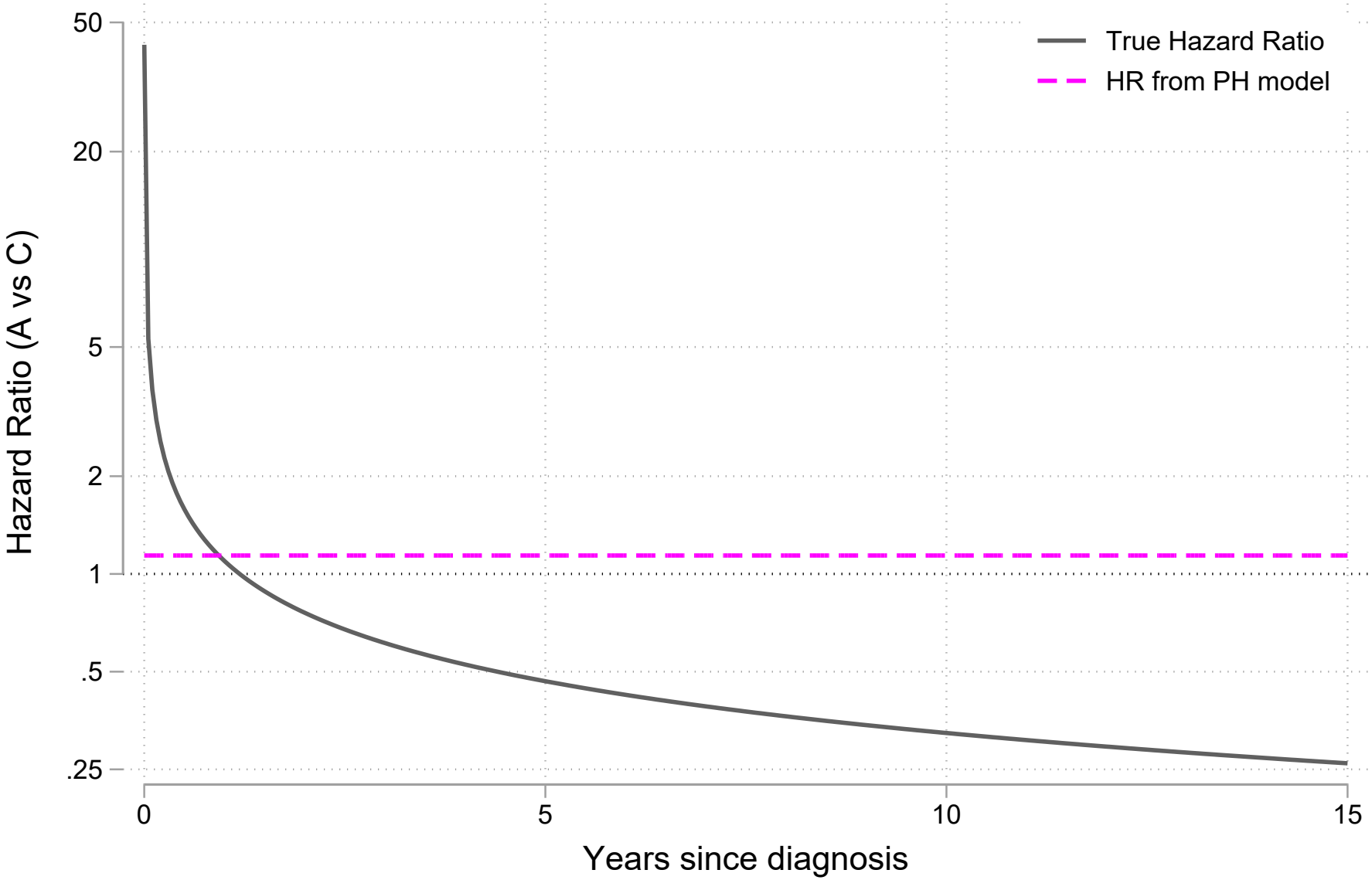
What about if we further extend the follow-up?



The two hazard functions



Hazard ratio for A vs C



Mathematical relations (for completeness)

$$
\begin{aligned}
S(t) &= \exp\left(-\int_0^t h(u)\,\mathrm{d}u\right) = \exp\left(-H(t)\right) \\
&\Updownarrow \\
-\frac{\mathrm{d}\log S(t)}{\mathrm{d}t} &= h(t)
\end{aligned}
$$

$H(t) = \int_0^t h(u)\,\mathrm{d}u$ is called the *integrated hazard* or *cumulative hazard*.

$$
h(t) = -\frac{\mathrm{d}\log(S(t))}{\mathrm{d}t} = -\frac{S'(t)}{S(t)} = \frac{F'(t)}{1-F(t)} = \frac{f(t)}{S(t)}
$$

What does this mean in practice?

- $h(t) = -\frac{\mathrm{d}}{\mathrm{d}t} \ln S(t)$
- In practical terms, this means that the event rate is proportional to the rate at which the survival function decreases.
- That is, if the survival function is decreasing sharply with time then the mortality rate is high (and vice versa).
- If the survival function is flat then the hazard is zero (and vice versa).
- The derivative of a function at a point is the slope of the [tangent to the] curve at that point. A curve that is decreasing (like the survival function) has a negative slope, hence the negative sign in the formula above.
- We can think of the hazard as being proportional to the rate of change of $S(t)$.

Relation between the survivor and hazard functions

$$
\begin{aligned}
h(t) &= \lim_{\Delta t \to 0} \frac{\Pr(\text{event in } (t, t+\Delta t] \mid \text{alive at } t)}{\Delta t} \\
&= \lim_{\Delta t \to 0} \frac{F(t+\Delta t) - F(t)}{S(t) \times \Delta t} \text{ where } F(t) = 1 - S(t) \\
&= \lim_{\Delta t \to 0} \frac{S(t+\Delta t) - S(t)}{\Delta t} \times \frac{-1}{S(t)} \\
&= \frac{\mathrm{d}S(t)}{\mathrm{d}t} \times \frac{-1}{S(t)} \text{ by definition of a derivative} \\
&= -\frac{\mathrm{d} \ln S(t)}{\mathrm{d}t} \text{ since } d/dx \ln(f(x)) = f'(x)/f(x)
\end{aligned}
$$

The proportional hazards assumption

- The Cox model (and many other survival models) assumes that the **ratio** of the hazard functions for any two patient subgroups (i.e., two groups with different values of explanatory variables) is constant over follow-up time.
- It is possible to fit a model that allows for non-proportional hazards.
- Note that it is the hazard **ratio** which is assumed to be constant. The hazards may vary freely with time.

Key take-home messages

- The PH assumption is a familiar assumption with a special name.
- Common regression models (e.g., linear, logistic, Cox) assume estimated effects are the same for all values of other covariates. Called either:
  - No interaction, or
  - No effect modification.
- The PH assumption is conceptually identical; covariate effects are the same for all values of time.
- Approaches for assessing and relaxing the PH assumption are conceptually the same as for covariate by covariate interactions. If the PH assumption doesn't hold, we can include time by covariate interactions.
- Since we don't estimate the effect of time in the Cox model, interactions with time are more complicated to fit.

Example of non-proportional hazards [1] Limited (D1) vs. extended (D2) lymph node dissection for gastric cancer

STATISTICS IN MEDICINE
Statist. Med. 2005; **24**:2807–2821
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.2143

Long-term survival with non-proportional hazards: results from the Dutch Gastric Cancer Trial

H. Putter[1,*,†], M. Sasako[2], H. H. Hartgrink[3], C. J. H. van de Velde[3] and J. C. van Houwelingen[1]

- Randomised study comparing the effect of an aggressive (D2) versus conservative (D1) surgical technique on cancer-specific mortality.

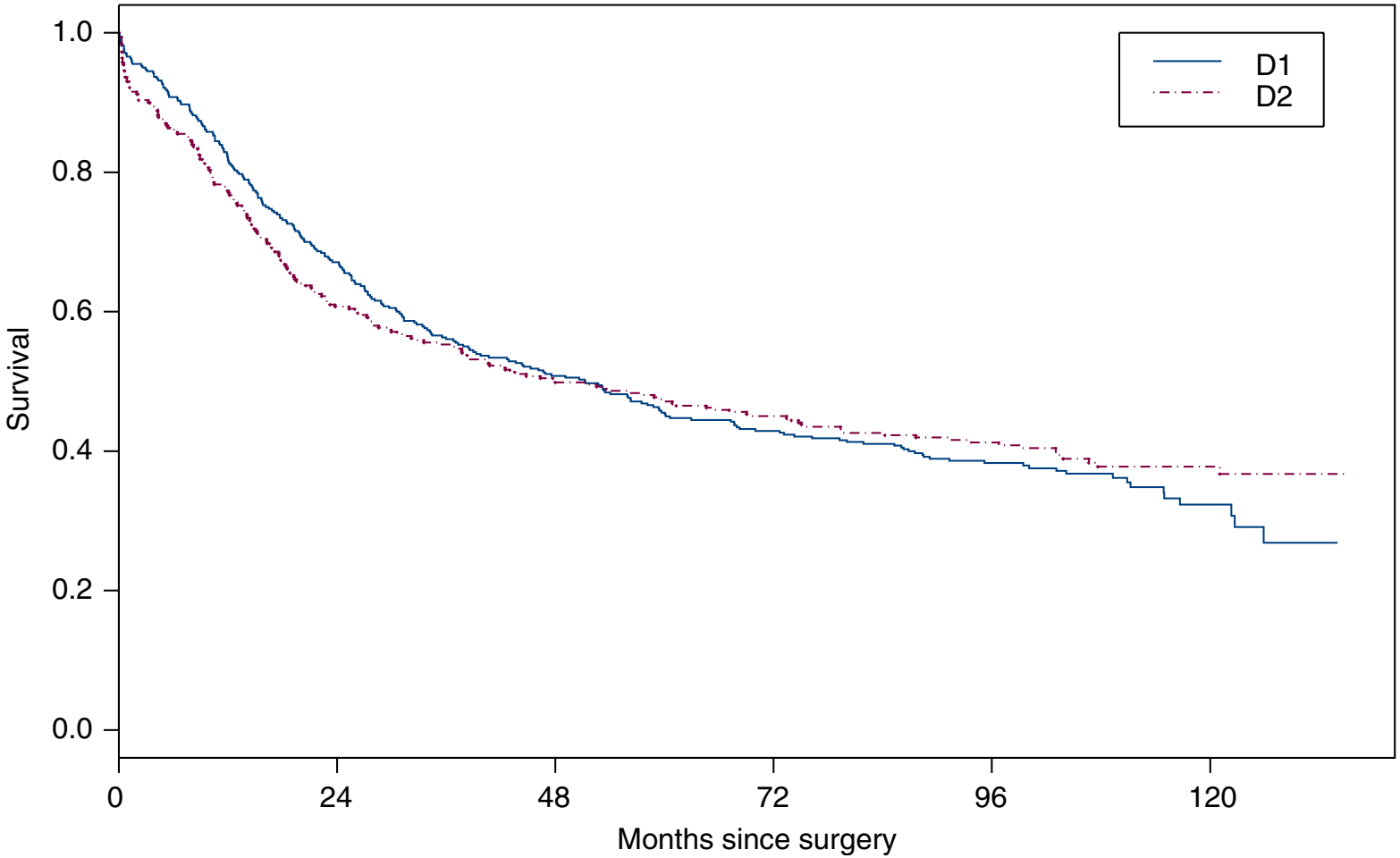


Figure 1. Kaplan–Meier plots of the survival curves for D1- and D2-dissection. The survival curves cross after 53 months.

The Cox regression with only randomization as a time-fixed effect gives an estimated hazard ratio of 0.97 of D2 dissection compared to D1-dissection, with a p-value of 0.73. The survival

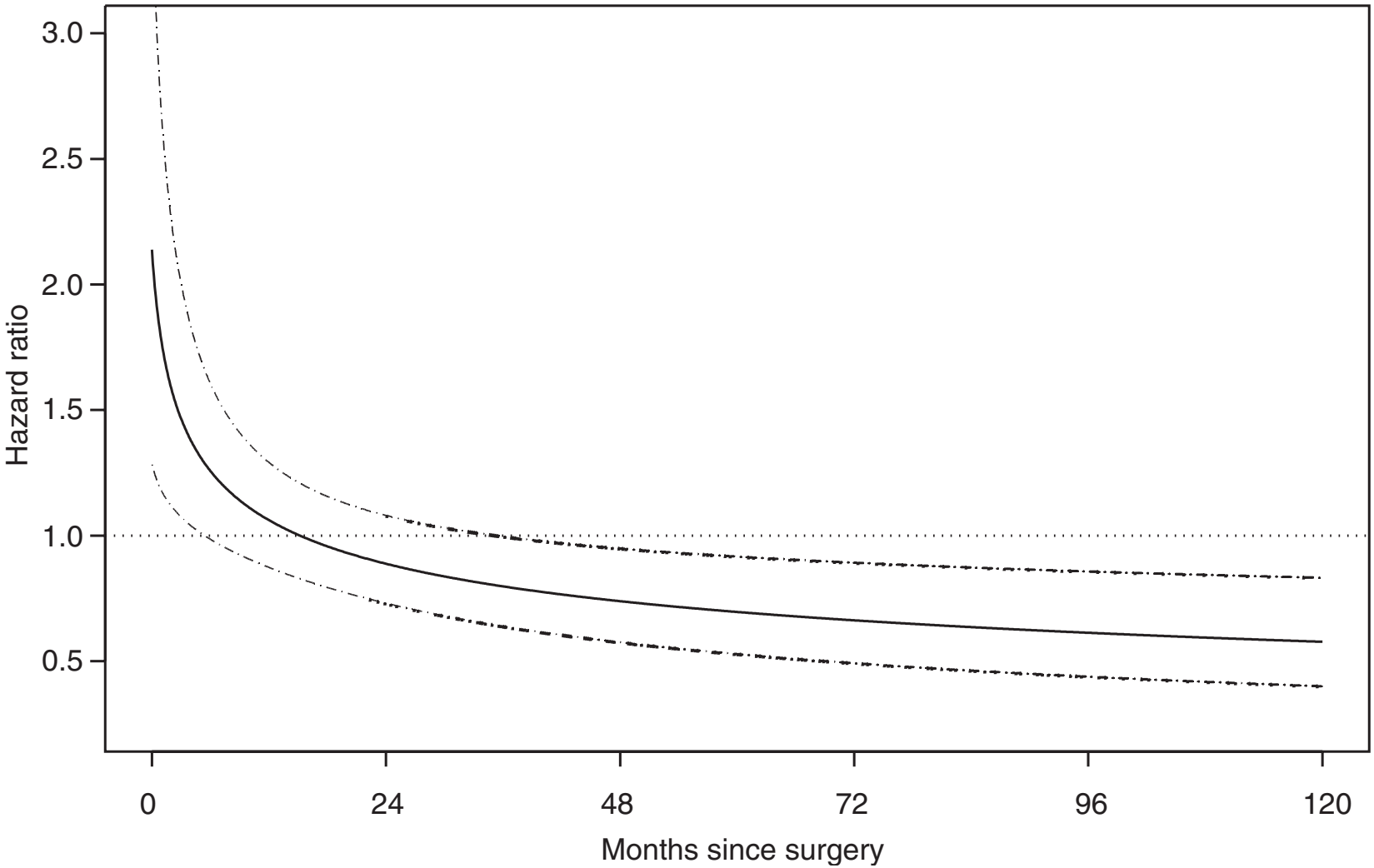


Figure 4. The estimated hazard ratio with 95 per cent confidence intervals based on Cox regression with treatment as time-dependent effect. A hazard ratio of one indicates equality of the hazard rates of D1 and D2.

Assessing the proportional hazards assumption

- `http://pauldickman.com/video/proportional-hazards/`
- Following is a list of some methods for assessing the appropriateness of the proportional hazards assumption (in increasing order of utility):
  1. Plotting the cumulative survivor functions and checking they do not cross. Not recommended, since the survivor functions do not have to cross for the hazards to be non-proportional.
  2. Plotting the log cumulative hazard functions over time and checking for parallelism.
  3. Plotting the log hazard functions over time and checking for parallelism.
  4. Including time-by-covariate interaction terms in the model and testing statistical significance.
  5. Plotting Schoenfeld residuals against time to identify patterns, and tests based on Schoenfeld residuals.

Assessing the proportional hazards assumption 2

- The first three methods do not allow for the effect of other covariates, whereas the second two methods do.
- Including a time-by-covariate interaction in the model has the advantage that we obtain an estimate of the hazard ratio as a function of time.

What to do if you have non-proportional hazards

- Non-PH is just another name for effect modification or interaction.
- Non-PH means you have different estimates of the HR at different points of time.
- Simply report the HR at selected time points (e.g., in a table) or a graph of the HR as a function of time.
- Disclaimer: assumes the HR is a sensible measure for your study design and research questiuon, you have fitted an appropriate model, and the differences in the HR are substantial (clinically and/or statistically).

Annals of Internal Medicine ORIGINAL RESEARCH

Risk for Arterial and Venous Thrombosis in Patients With Myeloproliferative Neoplasms

A Population-Based Cohort Study

Malin Hultcrantz, MD, PhD; Magnus Björkholm, MD, PhD; Paul W. Dickman, MSc, PhD; Ola Landgren, MD, PhD; Åsa R. Derolf, MD, PhD; Sigurdur Y. Kristinsson, MD, PhD*; and Therese M.L. Andersson, MSc, PhD*

Background: Patients with myeloproliferative neoplasms (MPNs) are reported to be at increased risk for thrombotic events. However, no population-based study has estimated this excess risk compared with matched control participants.

Objective: To assess risk for arterial and venous thrombosis in patients with MPNs compared with matched control participants.

Design: Matched cohort study.

Setting: Population-based setting in Sweden from 1987 to 2009, with follow-up to 2010.

Patients: 9429 patients with MPNs and 35 820 matched control participants.

Measurements: The primary outcomes were rates of arterial and venous thrombosis. Flexible parametric models were used to calculate hazard ratios (HRs) and cumulative incidence with 95% CIs.

Results: The HRs for arterial thrombosis among patients with MPNs compared with control participants at 3 months, 1 year, and 5 years were 3.0 (95% CI, 2.7 to 3.4), 2.0 (CI, 1.8 to 2.2), and 1.5 (CI, 1.4 to 1.6), respectively. The corresponding HRs for venous thrombosis were 9.7 (CI, 7.8 to 12.0), 4.7 (CI, 4.0 to 5.4), and 3.2 (CI, 2.9 to 3.6). The rate was significantly elevated across all age groups and was similar among MPN subtypes. The 5-year cumulative incidence of thrombosis in patients with MPNs showed an initial rapid increase followed by gentler increases during follow-up. The HR for venous thrombosis decreased during more recent calendar periods.

Limitation: No information on individual laboratory results or treatment.

Conclusion: Patients with MPNs across all age groups have a significantly increased rate of arterial and venous thrombosis compared with matched control participants, with the highest rates at and shortly after diagnosis. Decreases in the rate of venous thrombosis over time likely reflect advances in clinical management.

Primary Funding Source: The Cancer Research Foundations of Radiumhemmet, Blodcancerfonden, the Swedish Research Council, the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet, the Adolf H. Lundin Charitable Foundation, and Memorial Sloan Kettering Cancer Center.

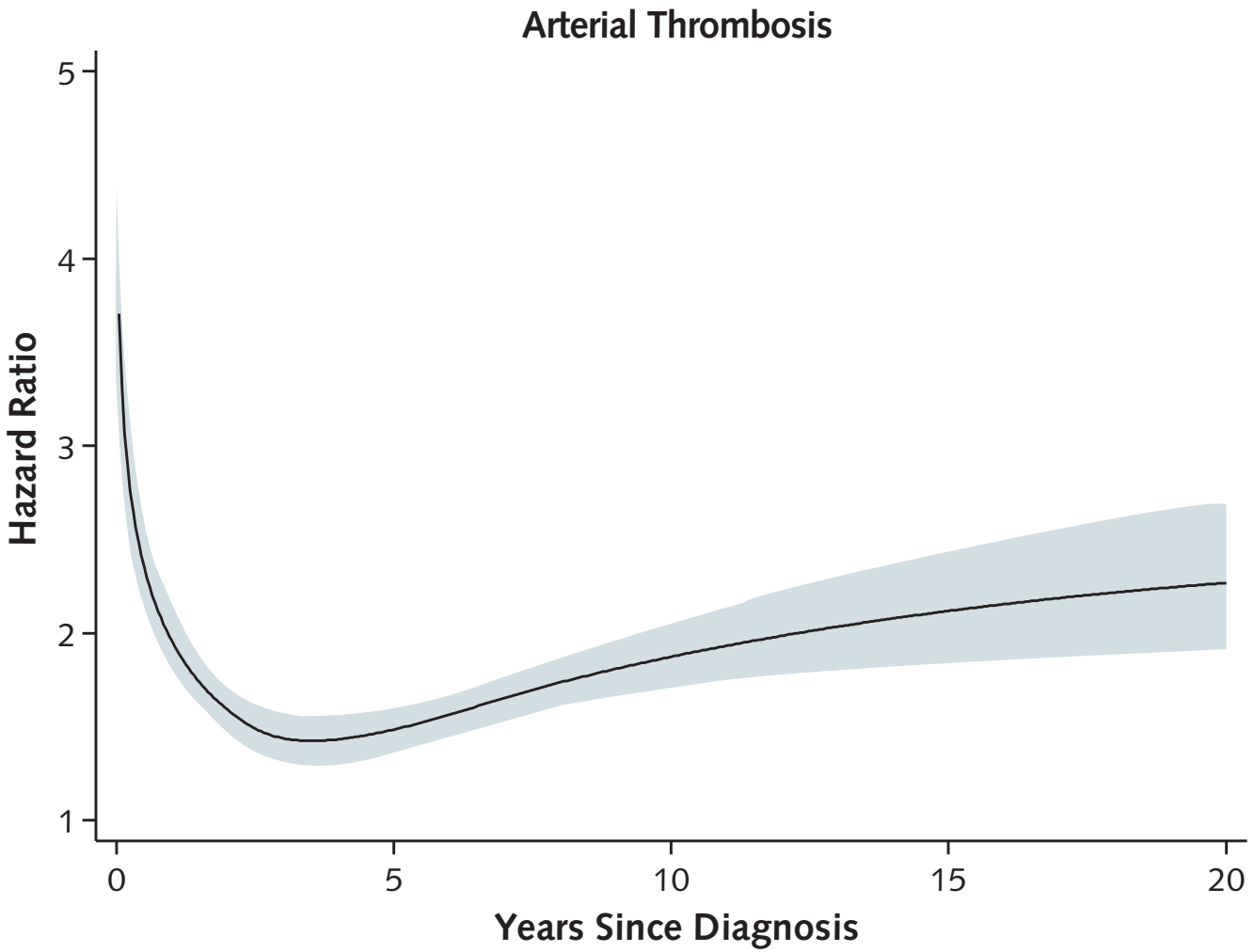
Ann Intern Med. 2018;168:317-325. doi:10.7326/M17-0028 **Annals.org**

For author affiliations, see end of text.

This article was published at Annals.org on 16 January 2018.

* Drs. Kristinsson and Andersson contributed equally to this work.

Figure 1. Arterial (*top*) and venous (*bottom*) thrombosis during follow-up in patients with MPNs versus matched control participants.



Sex differences in bladder cancer survival [3]

European Journal of Cancer 95 (2018) 52–58

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Bladder cancer survival: Women better off in the long run

Bettina Kulle Andreassen [a,*], Tom Kristian Grimsrud [a], Erik Skaaheim Haug [b,c]

- See Radkiewicz *et al.* (2020) [2] for a similar Swedish study.

Time-varying excess hazard ratio [3]

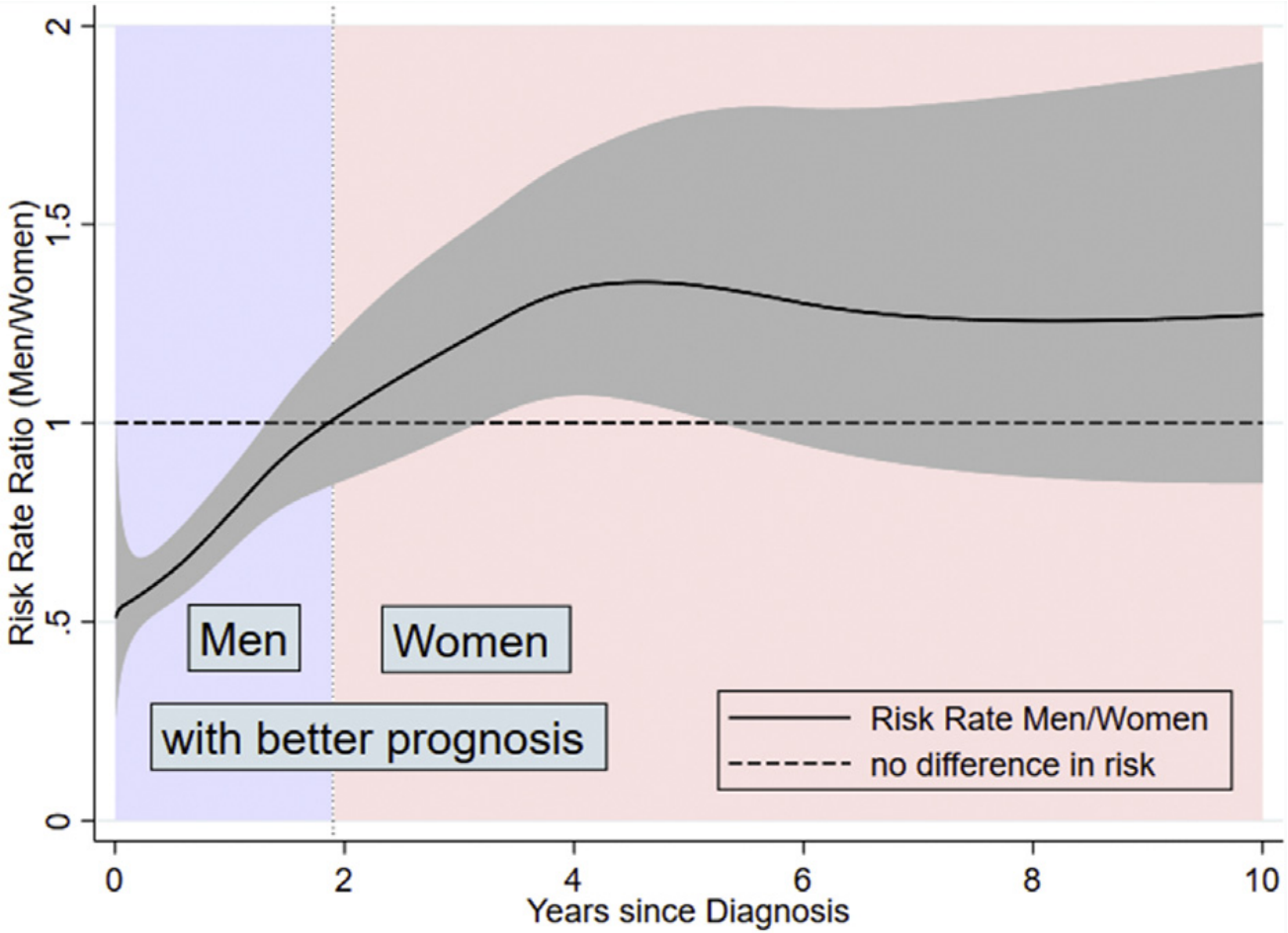
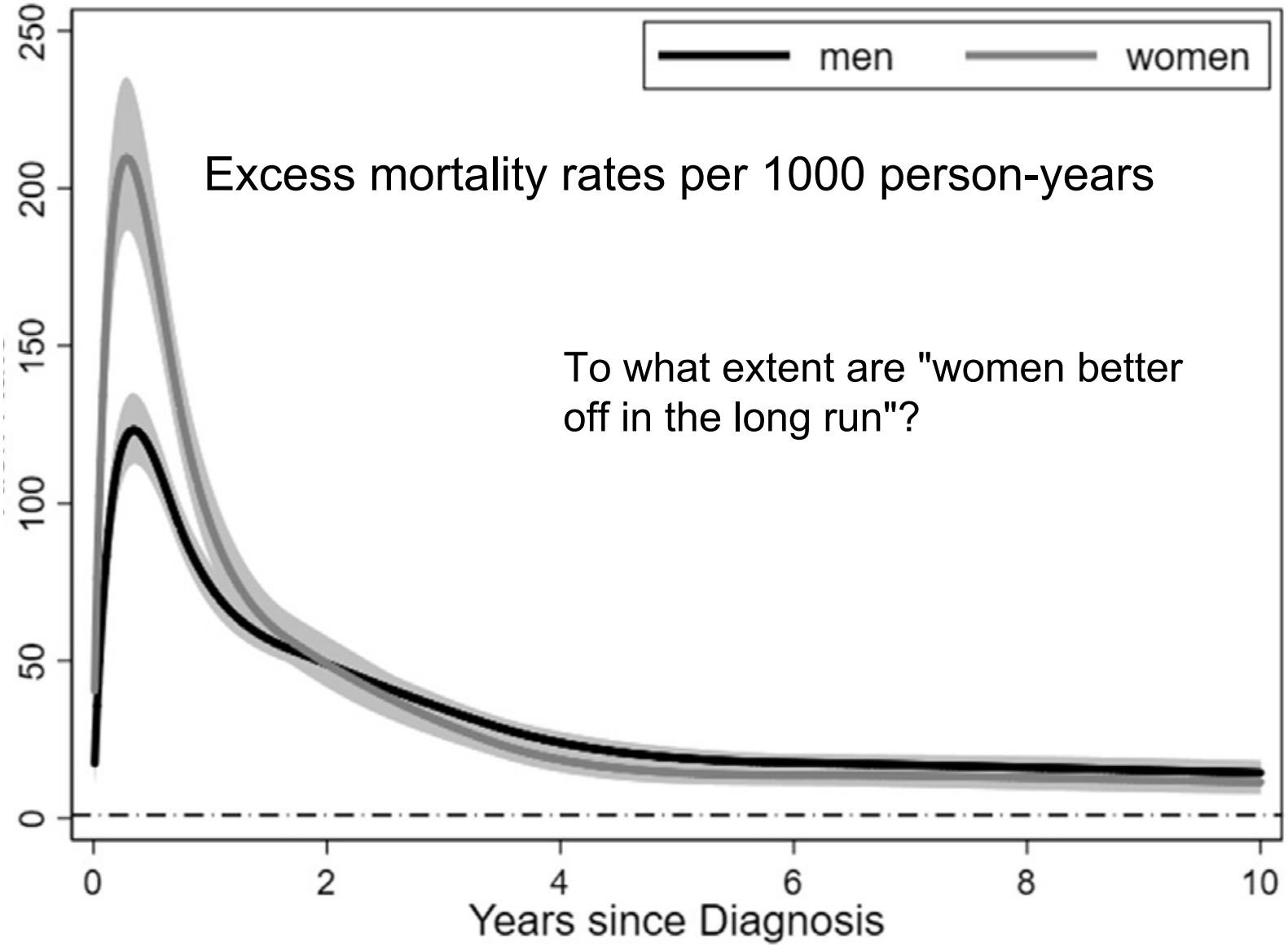


Fig. 2. Risk ratio (excess mortality rate ratio) including confidence intervals for men versus women with bladder cancer diagnosis. The

Baseline excess mortality rates [3]



Example in Stata

- 6,144 patients diagnosed with melanoma 1975–1994
- Outcome is death due to melanoma
- Interest is in the effect of sex on cause-specific mortality
- We will test the PH assumption for sex and fit a model that relaxes the PH assumption
- Code available at:
  `http://pauldickman.com/talk/proportional-hazards-cbb-march2022/melanoma.do`

Main effects model, Cox regression

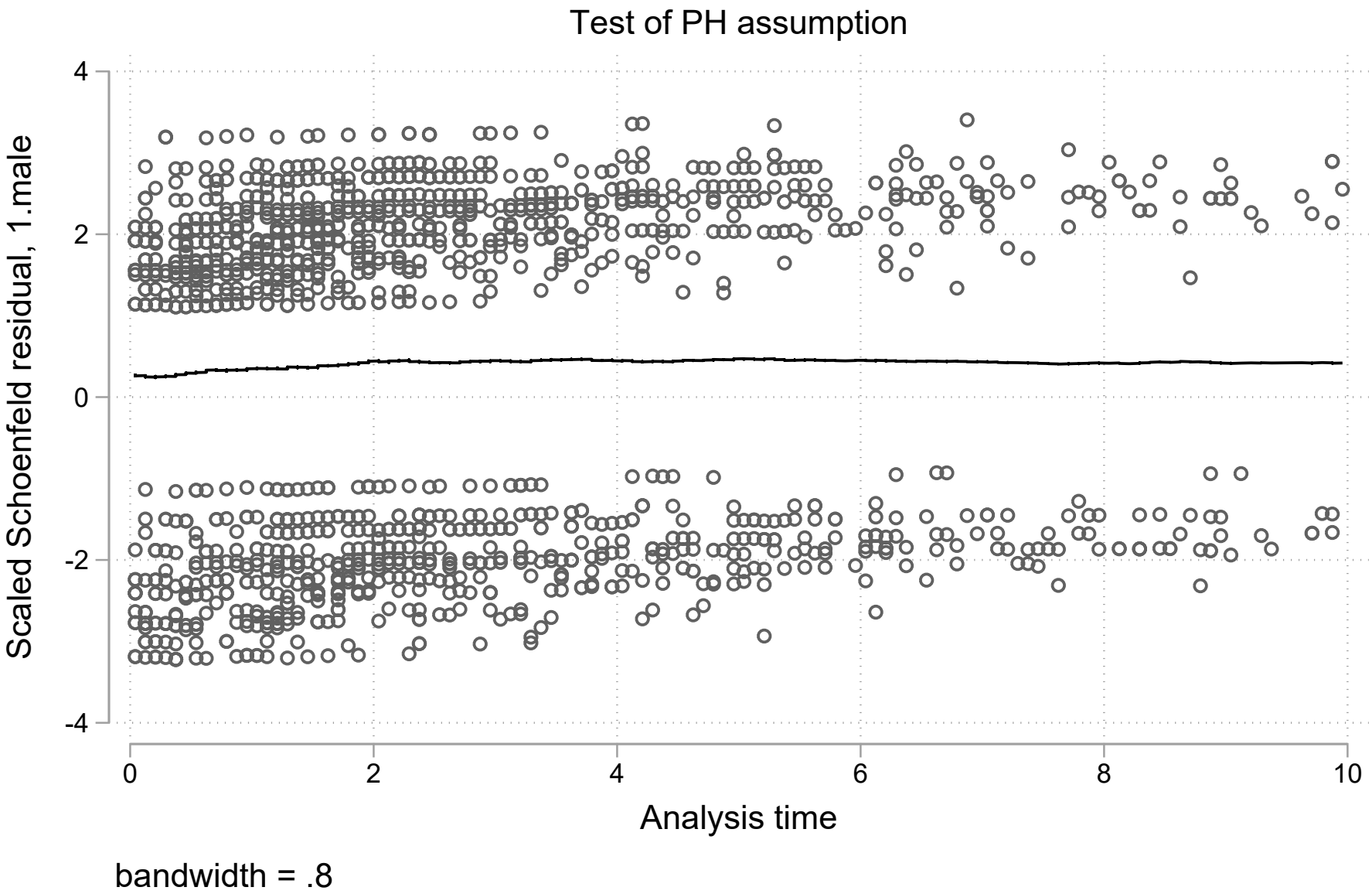
```
. stcox i.male i.period i.agegrp i.stage, noshow nolog
```

_t	Haz. ratio	Std. err.	z	P>|z|	[95% conf.	interval]
male						
Female	1	(base)				
Male	1.444224	.0756213	7.02	0.000	1.30336	1.600311
period						
Diag 75-84	1	(base)				
Diag 85-94	.8141348	.0419334	-3.99	0.000	.7359593	.9006144
agegrp						
0-44	1	(base)				
45-59	1.309861	.0962674	3.67	0.000	1.13414	1.512808
60-74	1.645387	.1173938	6.98	0.000	1.430663	1.892339
75+	2.478383	.2072222	10.85	0.000	2.103768	2.919705
stage						
Localised	1	(base)				
Regional	4.734787	.362295	20.32	0.000	4.075384	5.500883
Distant	13.53075	.8413382	41.89	0.000	11.97828	15.28443

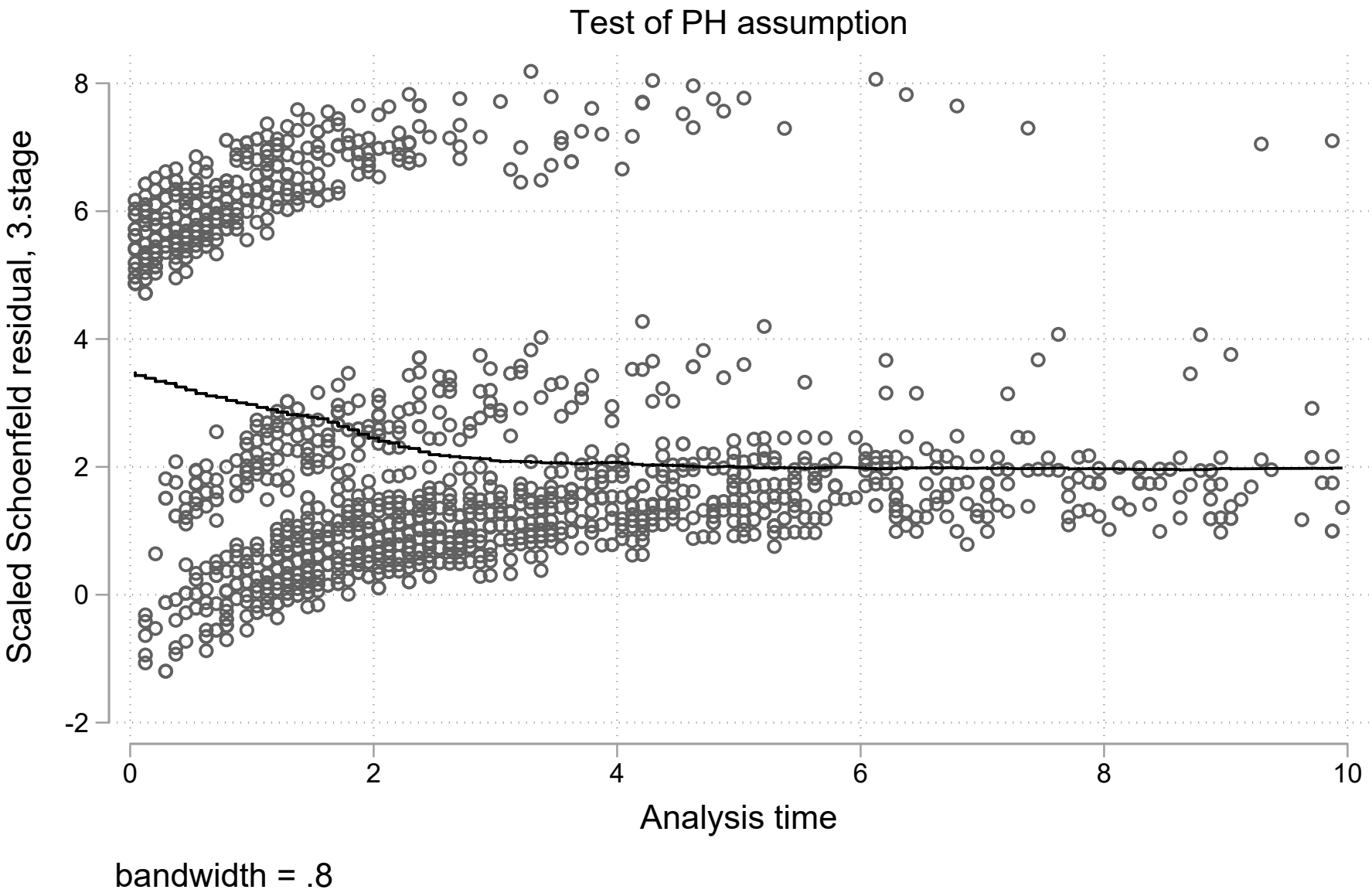
Test proportional hazards assumption

```
. estat phtest, detail

Test of proportional-hazards assumption

Time function: Analysis time
------------------------------------------------------------
             |        rho     chi2       df     Prob>chi2
-------------+----------------------------------------------
     0b.male |          .        .        1             .
      1.male |    0.02097     0.71        1        0.3980
   0b.period |          .        .        1             .
    1.period |   -0.02056     0.67        1        0.4116
   0b.agegrp |          .        .        1             .
    1.agegrp |    0.00095     0.00        1        0.9698
    2.agegrp |   -0.00636     0.06        1        0.8003
    3.agegrp |   -0.01351     0.29        1        0.5914
    1b.stage |          .        .        1             .
     2.stage |   -0.12275    23.35        1        0.0000
     3.stage |   -0.25130    87.87        1        0.0000
-------------+----------------------------------------------
 Global test |                 96.50        7        0.0000
------------------------------------------------------------
```

Plot of scaled Schoenfeld residuals on time (sex)



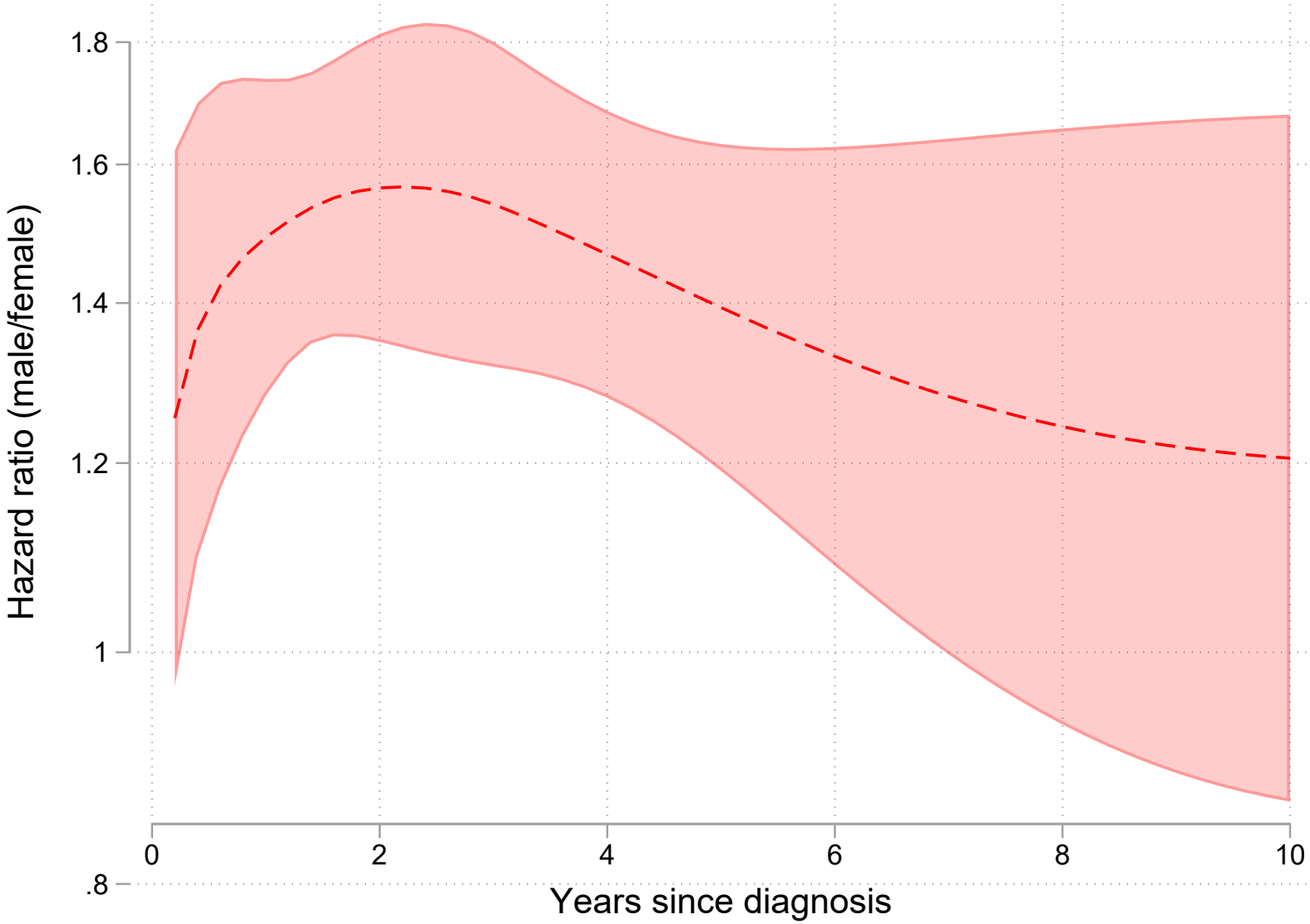
Plot of scaled Schoenfeld residuals on time (stage)



Relax the proportional hazards assumptiom for sex

```
. stcox i.male i.period i.agegrp i.stage, tvc(i.male) texp(_t) noshow nolog
------------------------------------------------------------------------------
          _t | Haz. ratio   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        male |
      Female |          1  (base)
        Male |   1.493613   .1232286     4.86   0.000     1.270606    1.755761
             |
      period |
Diagnosed 75-84 |          1  (base)
Diagnosed 85-94 |   .8144001   .0419567    -3.99   0.000     .7361821    .9009288
             |
             |    [output omitted]
       stage |
   Localised |          1  (base)
    Regional |   4.733842   .3622663    20.32   0.000     4.074497    5.499885
      Distant |   13.52508   .8413402    41.87   0.000     11.97264    15.27881
-------------+----------------------------------------------------------------
tvc    male |
      Female |          1  (base)
        Male |   .9877469   .0230544    -0.53   0.597     .9435791    1.033982
------------------------------------------------------------------------------
Note: Variables in tvc equation interacted with _t.
```

Estimated HR for sex as a function of time



Code for plot of time-varying HR on previous slide

```
. stpm2 male i.period i.agegrp i.stage, scale(h) df(5) eform tvc(male) dftvc(3)

. range temptime 0 10 51
. predict hr, hrnumerator(male 1) ci timevar(temptime)

. twoway (rarea hr_lci hr_uci temptime, color(red%25)) ///
>        (line hr temptime, sort lcolor(red)) ///
>       , legend(off) ysize(8) xsize(11) scheme(plotplain) yscale(log) ///
>        ytitle("Hazard ratio (male/female)") name("hrtvc", replace) ///
>        xtitle("Years since diagnosis")
```

References

[1] Putter H, Sasako M, Hartgrink HH, van de Velde CJH, van Houwelingen JC. Long-term survival with non-proportional hazards: results from the Dutch gastric cancer trial. *Stat Med* 2005;**24**:2807–2821.

[2] Radkiewicz C, Edgren G, Johansson ALV, Jahnson S, Häggström C, Akre O, *et al.*. Sex differences in urothelial bladder cancer survival. *Clinical genitourinary cancer* 2020; **18**:26–34.e6.

[3] Andreassen BK, Grimsrud TK, Haug ES. Bladder cancer survival: Women better off in the long run. *European Journal of Cancer* 2018;**95**:52–58.