Time-related Complexities in the analyses of observational Time-to-Event studies of Health: why do we need more Refined Statistical Methods?

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Focus of TG8: TIME = Change

- **STRATOS TG8 focuses on challenges specific to Survival (Time-to-Event) Analyses of longitudinal studies that Follow a Cohort over Time**
  usually to detect Associations of Predictors with Time to an Event (clinical endpoint, e.g. death)

- Yet, for >1,600 years [1] most philosophers agree that **the concept of (un-observed) TIME IS INHERENTLY LINKED to our Ability to OBSERVE CHANGE (i.e. Time is Defined by Change)**

[1] [St. Augustine's *Confessions* (Book 11) ca **AD 397**]

TIME = CHANGE

(**Lake Moraine, Canadian Rocky Mts.**
Site of the STRATOS Banff meeting excursion, July 2016)

2 Key Time-related Complexities

1) **Time-Varying Covariates** =

   Changes-over-Time in the Predictor VALUE

2) **Time-Dependent Effects** =

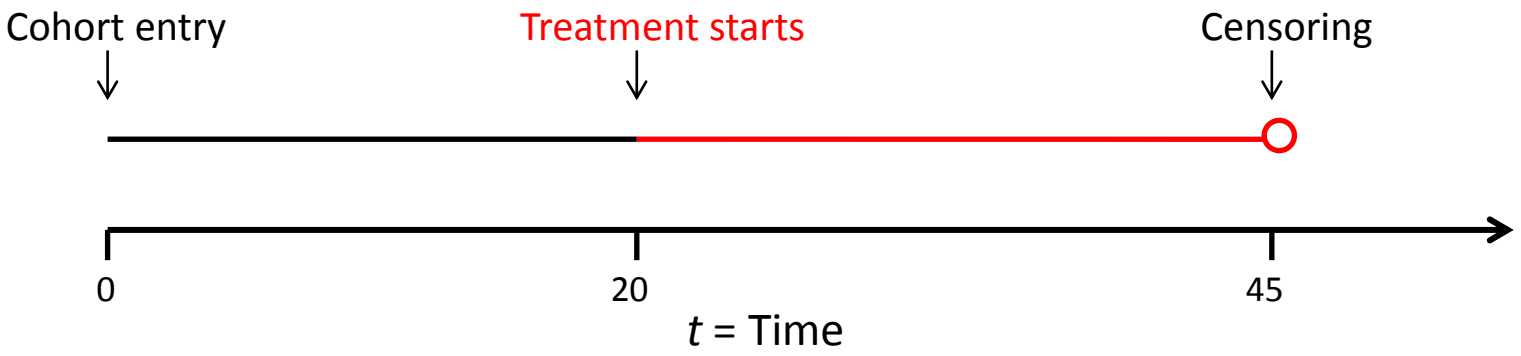
   Changes-over-Time in the Predictor EFFECT

PART 1: TIME-VARYING COVARIATES

The Simplest Example of TIME-VARYING COVARIATE:

Treatment (TX) **initiated DURING** the Follow-up

Treatment History for patient "i"



Data Setup (with Time-Varying Treatment A(*t*)) for patient "i"

Patient	Time Start	Time End	Age (yrs)	Current Treatment A(t)	Event
i	0	20	52	0	0
i	21	45	52	1	0

TIME-VARYING COVARIATES are Necessary to AVOID "IMMORTAL TIME BIAS"

- **Using Time-Fixed Covariate** (EVER Treated A=1 vs. UN-treated A=0) **to model Time-Varying Treatments, induces systematic BIAS toward a 'Protective' effect'** [Zhou et al *AJE* 2005; Suissa *AJE* 2008]

  This "**Immortal Time Bias**" [**Suissa, *AJE* 2008**] is **due to Mis-Classification of True Exposure (before Tx Initiation) by Time-Fixed covariates:**

  - **An Ever-Treated (A=1) subject** has (by definition) to 'survive' until his Tx Initiation time τ, i.e. **is effectively 'immortal' until time τ**
  - Yet, **Time-Fixed covariate, Incorrectly 'credits' this survival time to the Treatment group (A=1), even if the subject was UN-tread during that time (A(t)=0 for $0<t<\tau$)**

Example of Immortal Time Bias

[Tsoukas et al, *Arch Surg* 1998]

- Goal: To assess the potential **protective effect of Splenectomy** ("Exposure"= spleen removal) **against Mortality** (Outcome) **in HIV+ subjects** during the early phase of HIV epidemic

- Sample: N=45 HIV+ subjects
  30 splenectomised (including13 **(43%) after time 0**); 32 deaths

- **Results of 2 Cox models** (both adjusted for Age & CD4):

  1) Time-Fixed exposure (S=1 if subject ever splenectomised during follow-up, S=0 if Never):
     HR = 0.39 (95% CI: 0.17; 0.86), p = 0.02**

  2) Time-Varying exposure (*S(t)=1 only After splenectomy*)
     HR = 0.51 (95% CI: 0.23; 1.16), p = 0.11 (NS)

- **CONCLUSION: Time-Fixed model (1) Incorrectly suggests a Significant Protective effect of splenectomy due to Immortal Time Bias**

Need to use TIME-VARYING COVARIATES to AVOID Length Bias due to "using Future to predict Past"

- Another **example of Immortal Time Bias induced by Time-Fixed covariate:** paradox of "longer survival of Oscar winners", avoided with Time-Varying covariates (to get an Oscar one Has to Survive between ~10 and ~80 years) [Sylvestre et al, *Ann Int Med* 2006]

- More Complex **"Length Biases",** induced **if Time-Fixed covariates are Incorrectly used to model 'exposures' or risk/prognostic factors that Change DURING the Follow-Up:**

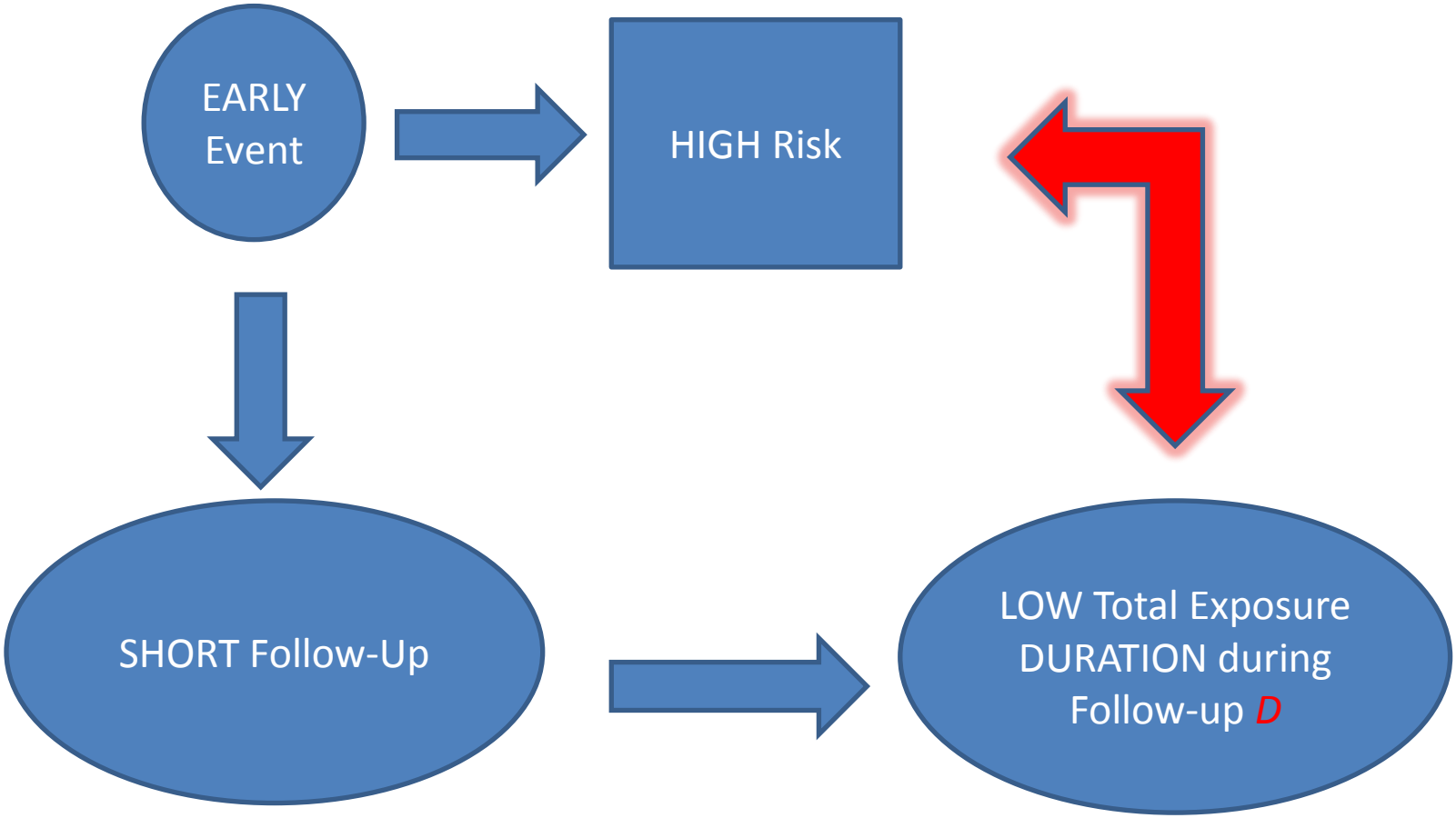
  - Example:
    Time-Varying covariates are necessary to avoid biased estimates of Cumulative Effects (e.g., *Exposure Duration or Cumulative Dose*)** [Abrahamowicz et al, *Stat Med* 2012]

** Modeling with Time-Fixed covariates = **"using Future to predict Past"**

Length Bias due to modeling Cumulative Exposure Duration as Time-Fixed covariate

Subject	Time interval (*t*)	Current Exposure *A(t)*	TIME-VARYING Cumulative Exposure Duration until end of Interval *D(t)*	TIME-FIXED Total Cumulative Exposure Duration until end of Follow-up *D*	Event
B	0-10	1	10	40	0
B	**10-20**	**0**	**10**	**40**	**0 (Survived day 20 with No event)**
B	20-30	1	20	40	0
B	30-40	1	30	40	0
B	40-50	1	40	40	0 (Censored at 50 days)
C	0-10	1	10	20	0
C	**10-20**	**1**	**20**	**20**	**1 (Event at day 20)**

Modeling Exposure Total Duration with **Time-FIXED covariate induces**
Spurious Association: LOW Duration ⇔ HIGH Risk (RED Arrow)



Length Bias due to modeling Cumulative Exposure Duration as a Time-Fixed covariate

- **Simulated EXAMPLE**

  (Data Simulated so that Longer Exposure Duration increases the Hazard of an Adverse Event):

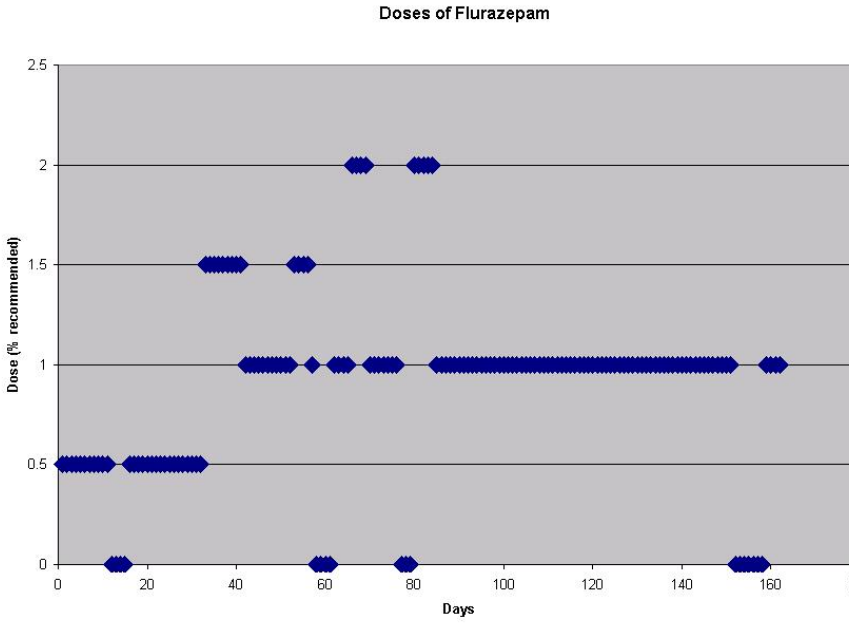
  - **Time-VARYING covariate *D(t)*: HR = 1.69 for 1 month Increase in Exposure Duration (until time *t*)**
    ⇒ Longer Duration ⇒ *Higher* Risk
  - **Time-FIXED covariate D: HR = 0.20 for 1 month Increase in (Total) Exposure Duration (over entire follow-up) (Incorrectly suggesting:**

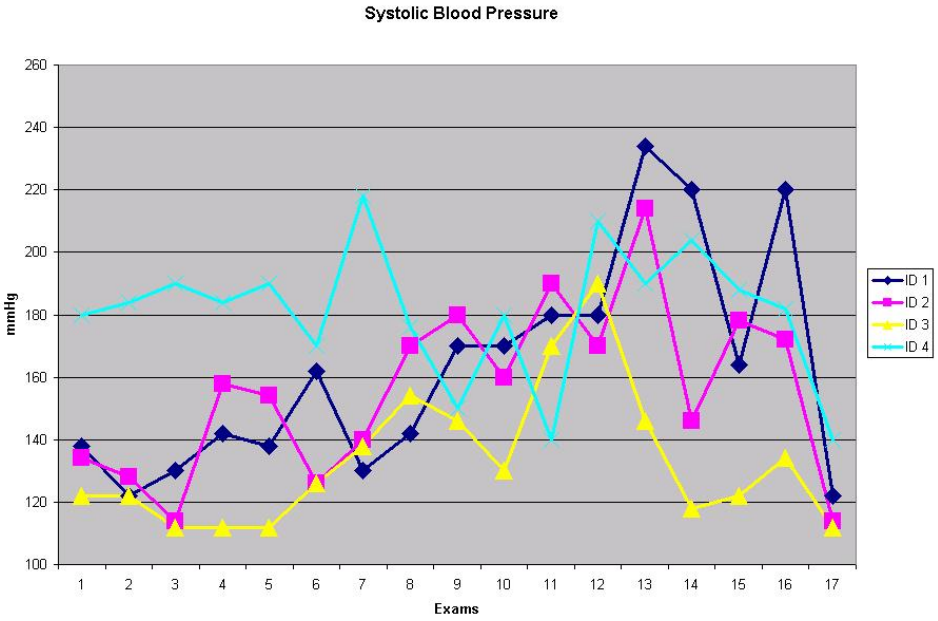
    Longer Duration ⇒ *LOWER* Risk)

2 Examples of more Complex Time-Varying exposures/risk factors:

LEFT: changes in **Dose of a Drug** **(over 180 days)** for 1 subject;

RIGHT: changes in **SBP** **(over 36 yrs)** in 4 Framingham Study subjects





Conceptual and Analytical CHALLENGES in Modeling Effects of COMPLEX TIME-VARYING Exposures

- **Challenge:**

  To Assess how the 'current' Risk (Hazard) at time T depends on the History of Past Values of Time-Varying Exposure ?
  [i.e. a Time-Vector: X(t) for $t \leq T$]

- **Conceptual Questions:**
  - **Do Past Values matter (e.g. Lagged or Cumulative effects)?**
  - **If Yes, what is the Relative Impact of Exposures that occurred at Different Times in the Past (e.g., Drug Doses taken 2 days ago Versus 30 days ago)?**

- **2-Step Solution:**
  1. **Define a Time-Varying Exposure metric M(T) that aggregates information on Past Values:**

     $$M(T) = f\,[X(1), X(2), \ldots X(T-1), X(T)]$$

  2. **Use standard regression methods (e.g. Cox model) with Time-Varying covariates to Estimate e.g. Hazard Ratio associated with M(T)**

Most recent Pharmaco-Epidemiology studies of Time-Varying drug exposures typically use Arbitrary Definitions of M(T)

- EXAMPLE:
  Mutually Incompatible, Arbitrary Definitions of M(T) used in 6 Different Studies of the SAME association between Oral Glucocorticoids Exposure & Risk of Infections [1-6]**:**
  - 'Current use'
  - 'Recent use'
  - 'Ever use'
  - 'Total past dose'

[1] Franklin J et al, *Ann Rheum Dis* 2007; [2] Lacaille D et al, *Arthritis Rheum* 2008;
[3] Smitten AK et al, *J Rheumatol* 2008; [4] Schneeweiss S et al, *Arthritis Rheum* 2007;
[5] Bernatsky S, Hudson M, Suissa S, *Rheumatology (Oxford)* 2007;
[6] Saag KG et al, *Am J Med* 1994]

Weighted Cumulative Exposure (WCE) model

[Abrahamowicz et al, *J Clin Epi* 2006; Sylvestre & Abrahamowicz, *Stat Med* 2009; Xiao et al *JASA* 2014 (extension to MSMs with IPT weights)]

- To avoid the need for arbitrary selection of M(T) metric, we proposed a more general model: **(recency-)Weighted Cumulative Exposure (WCE) model**, where the **Cumulative Effect of Past Exposure History, on the Current Hazard, is modeled as Weighted Sum of Past Doses:**

$$WCE(u) = \sum_{t \le u} w(u-t) * X(t)$$

u = current time (when Risk is being assessed)
WCE(u)= Weighted Cumulative Effect of Past Doses (Time-Varying)
X(t) = *D*ose at time *t* ($t \le u$)
u-t = *T*ime elapsed since Dose *X(t)* was received
w(u-t) = Weight Function (describing Relative Importance of Dose *X(t)* as a function of Time Elapsed (*u-t*))

- The Weight Function is estimated (directly from the data) using Flexible Cubic Splines, which avoid the need to specify *a priori* its shape (or analytical form) [**Sylvestre & Abrahamowicz 2009****; Xiao et al, 2014]

** **R package implementing flexible WCE analyses: http://cran.rproject.org/web/packages/WCE**

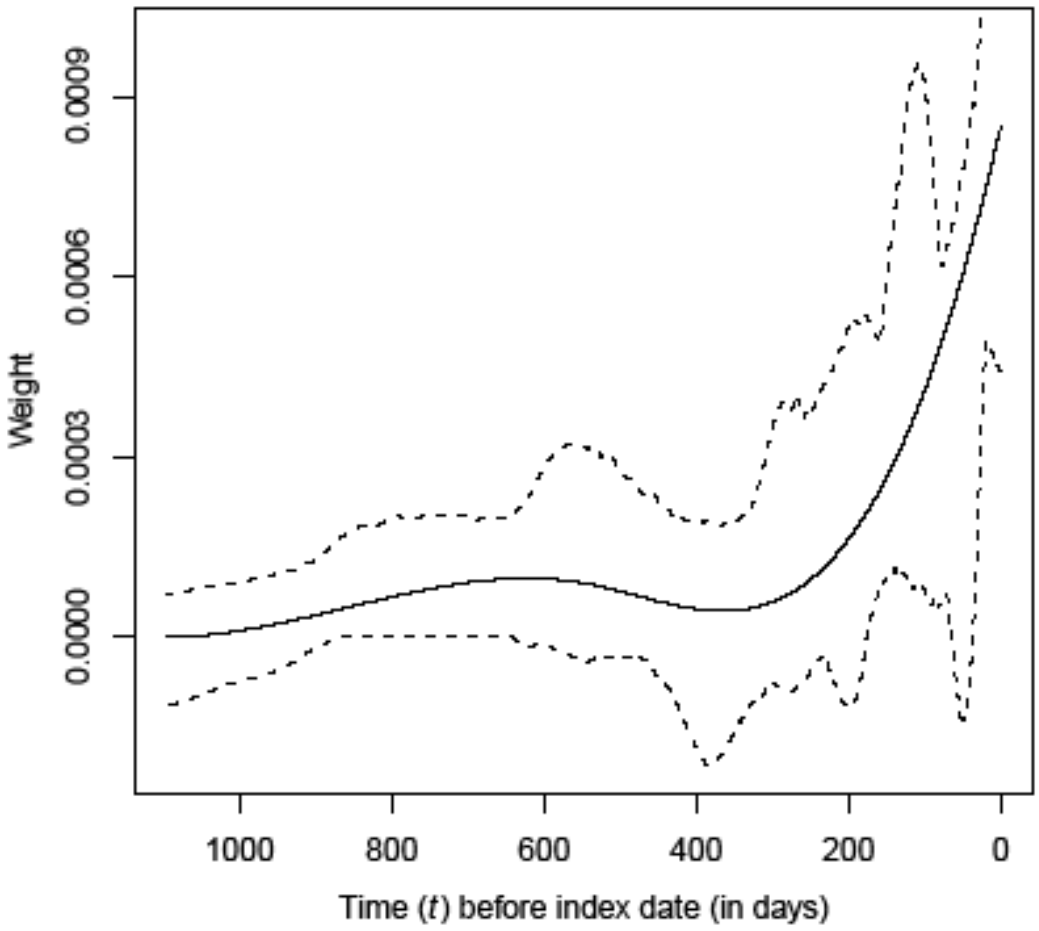
Example of Application of WCE: use of oral Glucocorticoids (GC) vs. risk of serious Infection in rheumatoid arthritis (RA)

- Objective: To explore **how the risk of serious infection depends on current and prior oral GC therapy in N= 16,207 elderly (>65 yr) RA patients** (Quebec, Canada, 1985-2003)*
- **Nested case-control** design: **1,851 cases** of serious infection
- Analyses adjusted for several potential confounders
- **WCE model fit much better** than any of the 10 'conventional' Cox models with different time-varying exposure metrics M(T)**
  (** AIC lower by 29 to 140 points)

  [**Dixon, Abrahamowicz, Beauchamp et al**, *Ann Rheum Diseases* 2012]

* Data from *W. Dixon* (Manchester, UK) & *S. Bernatsky* (McGill)

WCE-based **Weight function** for the association of prior GC exposure with serious infection:
(**expected) SHORT-Term impact on Innate Immune System** (use in the last 3-6 months) **&**
(unexpected) LONG-Term impact on Adaptive Immune System (use 1.5-2.5 yrs ago) [1] **?**
[1] = [McMaster & Ray, *Nat Clin Pract Endocrinol Metab* 2008]



WCE Estimates of Adjusted Odds Ratios for the associations of **Various Patterns of Past GC therapy** with **Current Infection** Risk

Pattern of use	**Reference**	**OR * (95% CI)**
Current user, 5mg, for last 7 days	Non-user	1.03 (1.02, 1.10)
Current user, 5mg, for last 28 days	**Non-user**	**1.11 (1.07, 1.26)**
Current user, 5mg, for last 3 months	**Non-user**	**1.33 (1.21, 1.46)**
Current user, 5mg, for last 3 years	**Non-user**	**2.05 (1.77, 2.32)**
Past user, 5mg, for 6 months, stopped 6 months ago	Non-user	*1.09 (0.97, 1.26)*
Current user, 30mg, for last 28 days	**Non-user**	**1.92 (1.50, 4.05)**
Current user, 30mg, for last 3 months	**Non-user**	**5.51 (3.17, 9.54)**
2 CONVENTIONAL Time-Varying Cox Models:		
1/ CURRENT User (any exposure duration, any dose)	Non-user	**1.85 (1.65, 2.08)**
2/ EVER User (use at any time in past/present, any duration, any dose)	Non-user	**1.66 (1.47, 1.88)**

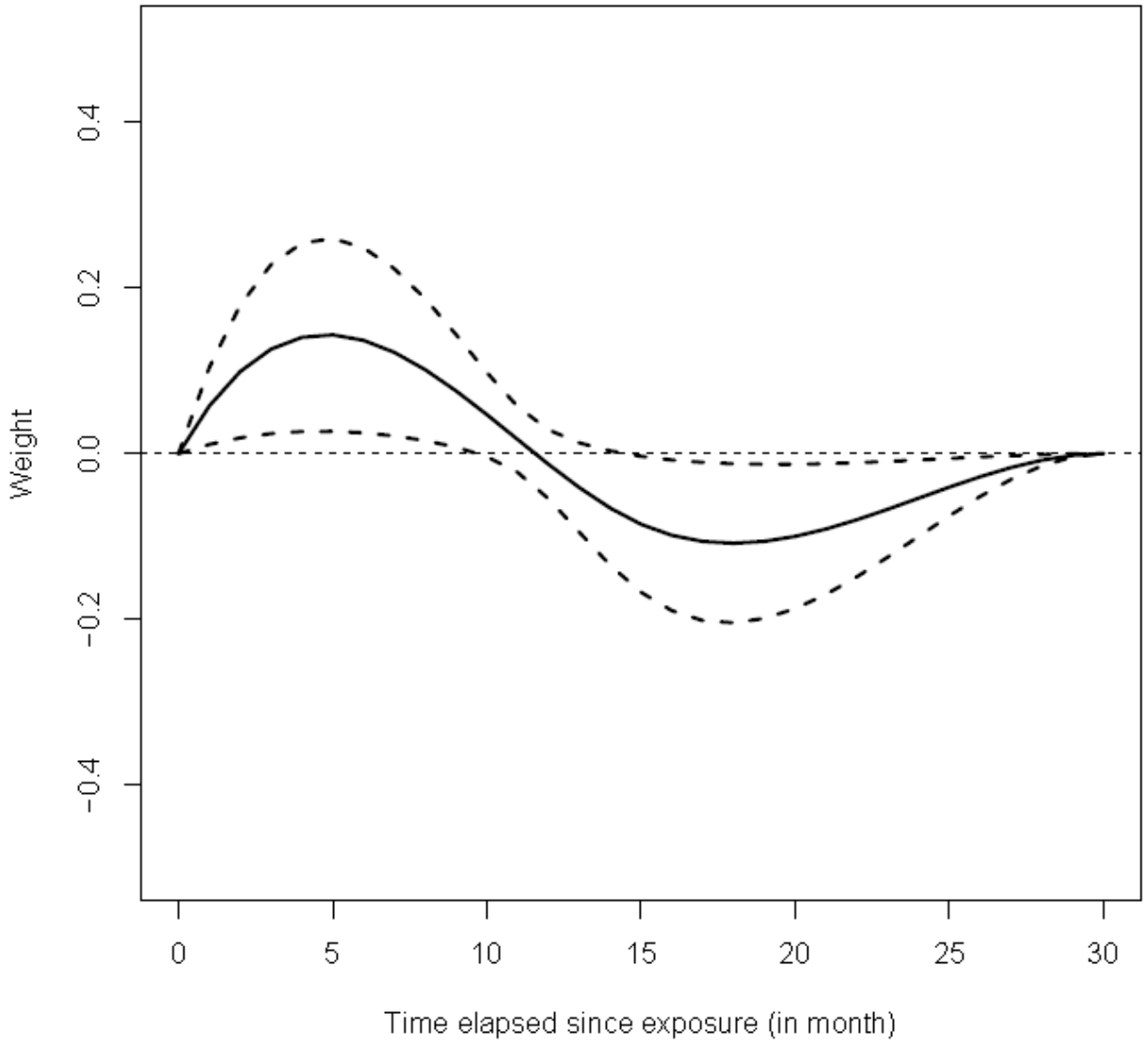
* Odds Ratio for the relative 'risk' of infection for the pattern of use in the 1st column compared to the reference pattern of use in the 2nd column.

2nd WCE Application (Marginal Structural Models): Didanosine (DDI) use vs. Cardiovascular (CVD)Risks in HIV

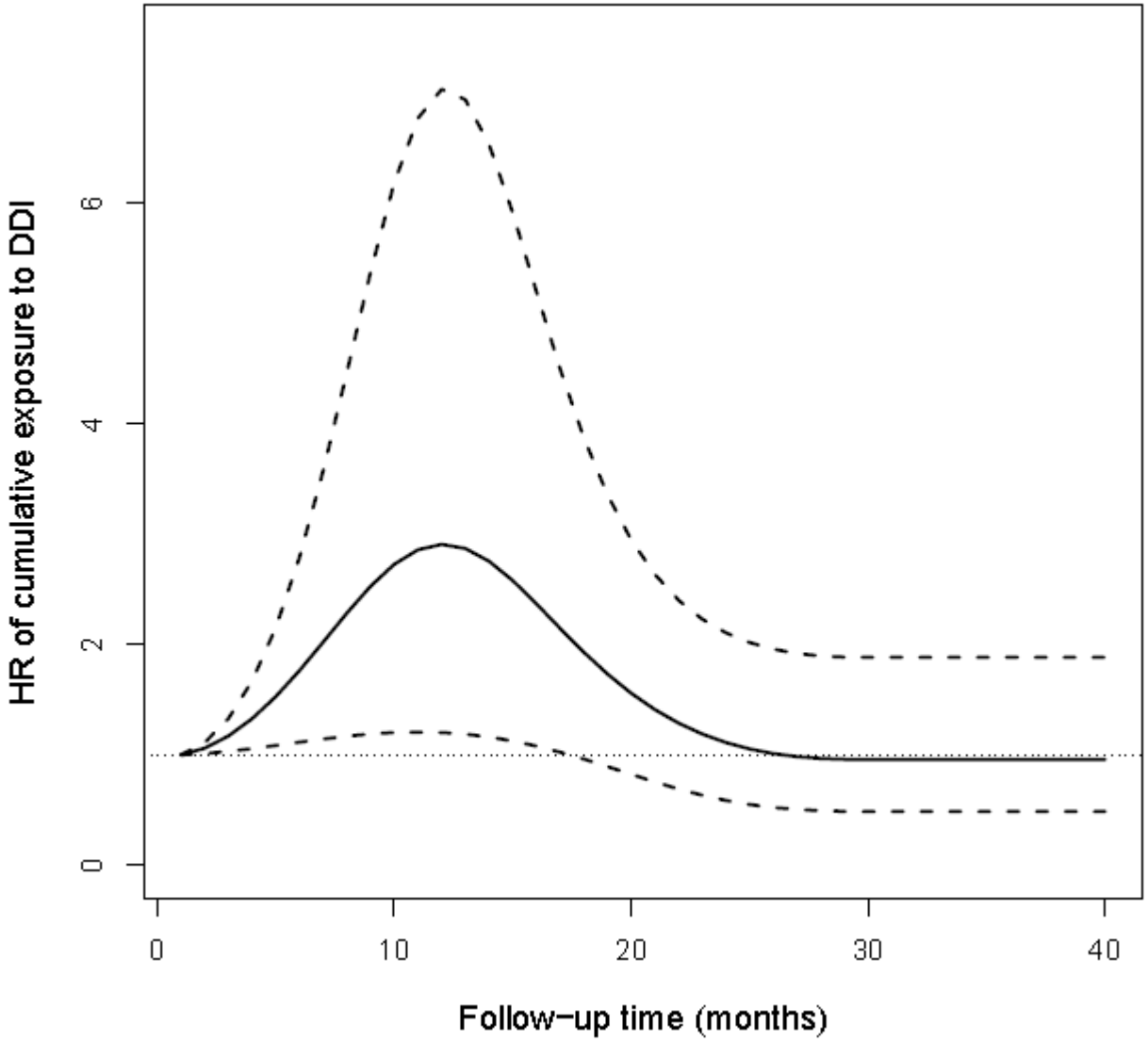
- **Background**: **Inconsistent recent results** [Lang et al, *Arch Int Med* 2010; Worm et al, *J Infect Dis* 2010] re: potential **Increased Cardiovascular (CVD) Risks** with use of **Didanosine (DDI)** (an Nucleoside Analog Reverse Transcriptase Inhibitor (NRTI)) [**Sabin et al, *Lancet* 2008**]
- **Objective**: **To re-assess the impact of DDI use on CVD risks in 11,625 patients in Swiss HIV Cohort (with 350 CVD events** in up to 12 yrs of follow-up)
- **Methods**: **Marginal Structural Models (MSM)** with IPT weights to account for monthly measurements of time-varying confounders (CD4 cells, RNA)
- **Results** [Xiao et al, *J Am Stat Assoc (JASA)* 2014; Young et al, *J AIDS* 2015]**:**
  - **Conventional Cox MSM's with different simple time-varying metrics** of DDI exposure (current use, recent use (past 6 months), total (un-weighted) duration) **all yielded Non-Significant Estimates (95% CI for HR included 1)**
  - **In contrast, our WCE Cox MSM fit the data much better** (AIC lower by ~ 10 points) than any conventional model) **and Significantly (p<0.01) better than MSM that assumed No DDI effect**
  - **WCE estimates suggested a Complex "Dual" effect** of Past DDI exposure, which helped explain inconsistencies in previous publications** (** risk *Increase* associated with Current/Recent use in past 12 months *versus* risk *Decrease* associated with Past use, 12-24 months ago)

Weight Function (WCE MSM) for "Dual effect"** of past DDI use on CVD risks

(risk *Increase* associated with Current/Recent use in past 12 months *versus* risk *Decrease* for Past use, 12-24 months ago)**



Estimated **Total Cumulative Effect (HR) of Being Always Treated with DDI** (*versus* Never treated) **as a function of Treatment Duration** (**WCE MSM model**)



Part 2: TIME-DEPENDENT EFFECTS

Cox's PH model

- In 1972, (now) Sir David R. Cox published *Regression models and life tables* in the Journal of Royal Statistical Society (*JRSS, series B*)
- By 2002, this paper had been cited in >17,000 articles
- Indeed, the Cox's Proportional Hazards (PH) regression model has become a standard method for survival (time-to-event) analyses
- Yet, the PH model is usually selected *a priori* and the underlying PH assumption is rarely tested**

(** E.g., among the 43 multivariable **survival analyses published in top cancer journals** in early 1990's, **>97% (42/43) relied on Cox PH model**, but ONLY <5% (2 of 42 papers) reported testing the PH hypothesis
[Altman et al, *Br J Cancer* 1995])

Proportional hazards (PH) model:

$$\lambda(t, X) = \lambda_0(t)\exp(\beta X)$$

where:

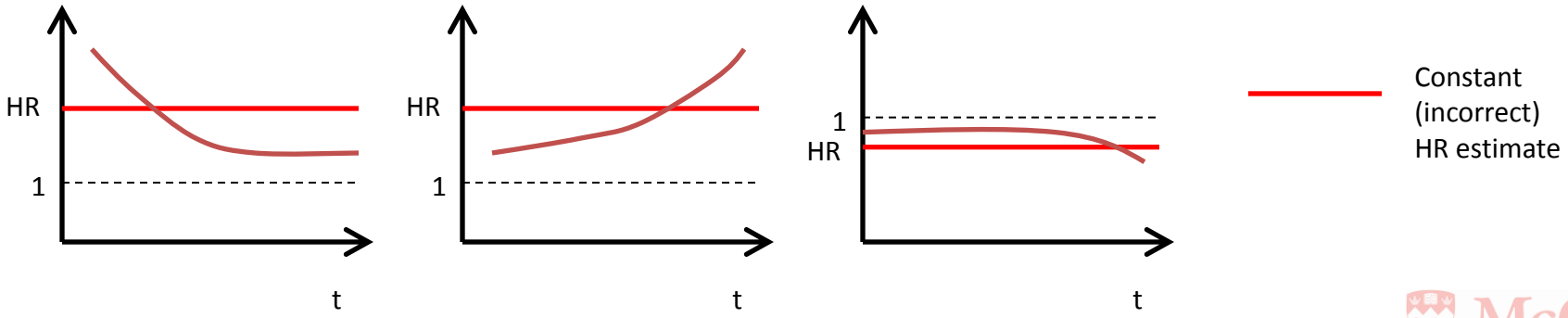
X	covariate vector, which may include Time-Varying Covariates *X(t)*
$\lambda_0(t)$	baseline Hazard function (for the 'reference group' with *X=0*)
$\lambda(t, X)$	conditional hazard, for subjects with a given covariate vector *X*
β	regression parameter vector = log (Hazard Ratio)

- Important **Proportional Hazards assumption**:
  - Hazard ratios are Constant over time, i.e. covariate effects on the hazard do Not change during the follow up (PH assumption)

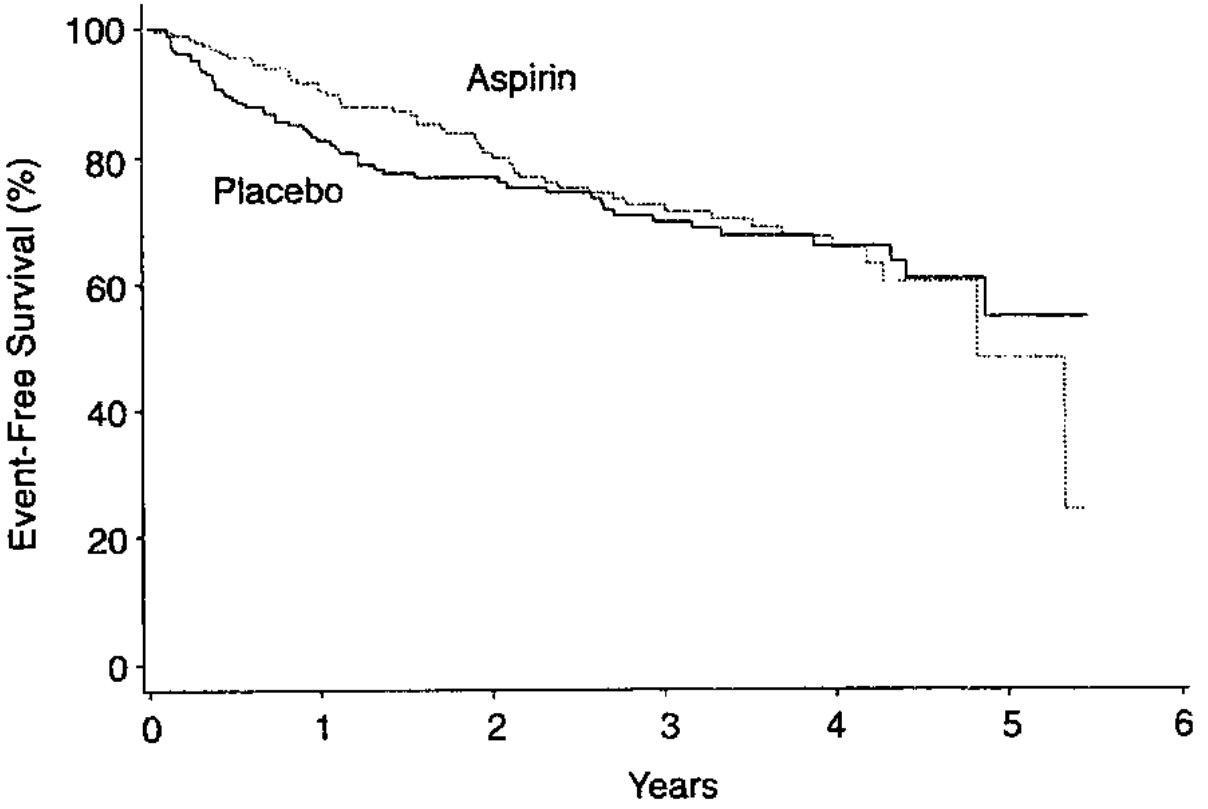
Why Proportional Hazards (PH) assumption may be incorrect in many applications?

- <u>Some reasons why Hazard Ratio (HR) may Vary over Time:</u>
- Design limitations
  - Inherently Time-dependent covariates are measured at baseline only, and used to predict outcomes over long follow-up (*HR Decreases* toward Null?)

    (e.g., does serum cholesterol measured today will predict cardiovascular mortality in the next 15 years equally well as in the next 5 years?)
- Impact of a chronic disease (binary variable) on the hazard increases with increasing damage (HR *Increases* over time?)
- Lagged effect of treatment (*HR initially close to null* (HR=1) *then Decreases* reflecting *Long-Term Protective effect*?)



REAL-LIFE EXAMPLE of **PH Violation** (converging KM curves): **Early Protective Effect of ASA, against CVD, Lasts Only <2 yrs**



Cote, Battista, Abrahamowicz et al, *Ann Int Med* 1995 (RCT of Aspirin vs. Placebo, for preventing CVD in Asymptomatic pts with Carotid Bruits)

Overview of (selected) methods to Test and/or Account for potential Violations of the PH hypothesis

- In the last 3 decades, statisticians proposed Dozens of Tests to formally test the PH hypothesis (see e.g. reviews by [Ng'andu, *Stat Med* 1997] and [Grant et al, *Lifetime Data Anal* 2014])
- More **recent Methods allow not only testing the PH hypothesis** (separately for each predictor) but, in the case of its being rejected, also **Flexible Modeling of the TIME-DEPENDENT (TD i.e. Non-PH) Predictor Effects on the Hazard (i.e. Changes over Time in HR**)
- Alternative **Flexible TD extensions of the Cox model** were proposed by:
  - Zucker & Karr, *Ann Stat*, 1990
  - Gray, *JASA*, 1992
  - Hastie & Tibshirani, *JRSS*, 1993
  - Grambsch & Therneau, *Biometrika* 1994
  - Hess, *Statistics in Medicine*, 1994
  - Verweij & Houwelingen, *Biometrics*, 1995
  - Kooperberg, Stone, Truong, *JASA*, 1995
  - Abrahamowicz, MacKenzie, Esdaile, *JASA*, 1996
  - **Therneau TM & Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer, New York, 2000. (MONOGRAPH)*****

*** with **Comprehensive User-Friendly R Software package** that implements PH tests and flexible TD modeling:

Therneau T. *survival: A Package for Survival Analysis in S,* version 2.39. R package, 2016, http://CRAN.R-project.org/package=survival.

Example of a flexible Time-Dependent (non-PH) model

Cox PH model:

$$\lambda(t, X) = \lambda_0(t)\exp\left(\sum_j \beta_j X_j\right)$$

TIME-DEPENDENT (TD) HAZARD RATIO model:*

$$\lambda(t, X) = \lambda_0(t)\exp\left(\sum_j \beta_j(t) X_j\right)$$

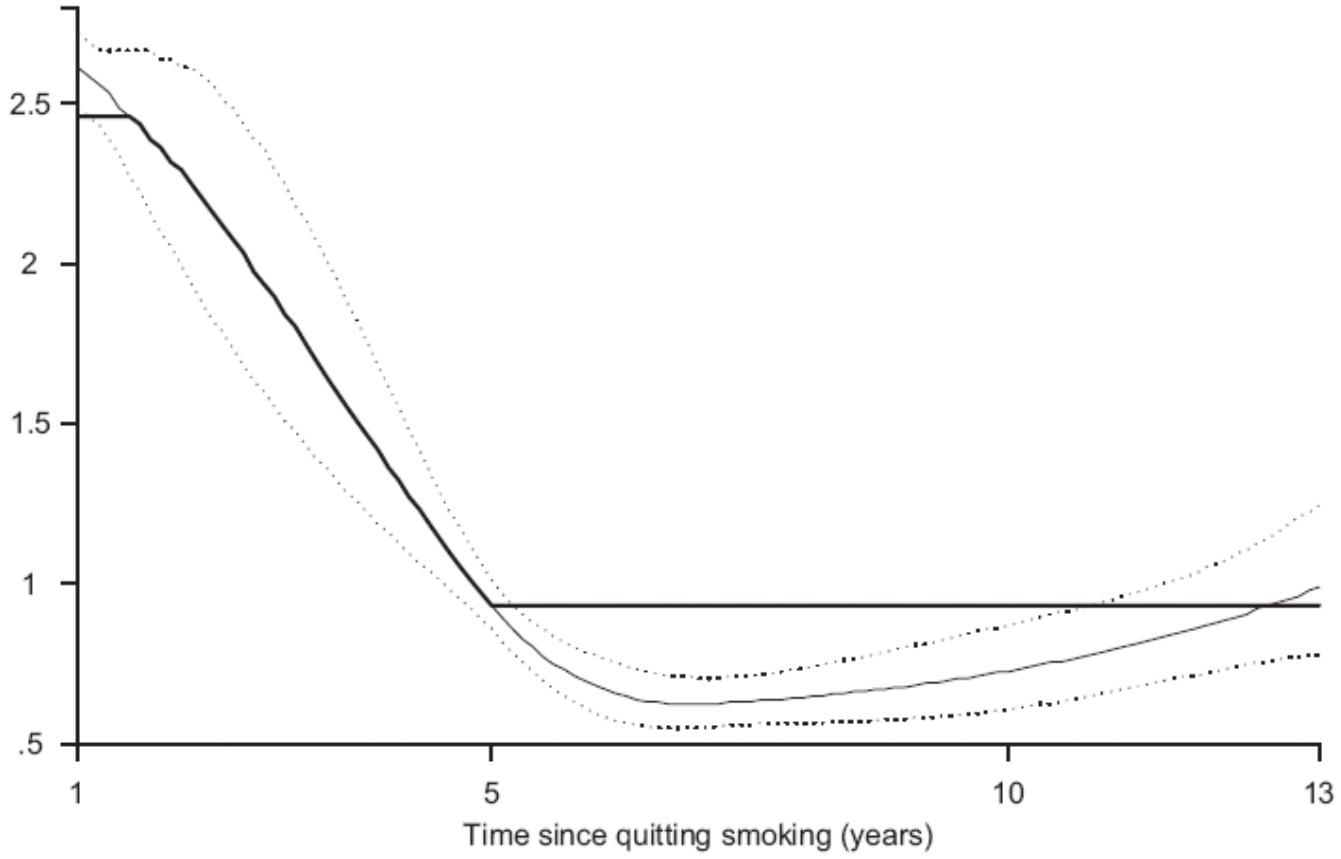
where: **the time-function $\beta_j(t)$ = estimate of the Time-Dependent (TD) effect of predictor X_j** (*log Hazard Ratio at time t*),

$\beta_j(t)$ is modeled using flexible quadratic regression B-splines,
to avoid the need to *a priori* specify the shape or pattern of changes over time in the predictor's effect on the hazard

* **[Abrahamowicz, MacKenzie, Esdaile, *J Am Stat Assoc (JASA)* 1996]**

Example of a TD effect:

HR(t) of Cardiovascular Events for Ex-Smokers vs. Never-Smokers Decreases fast with Increasing Time-since-Smoking-Cessation



[Rachet, Abrahamowicz, Sasco, et al. *Statistics in Medicine* 2003]

Different Patterns of TD Effects of Prognostic Factors for Mortality in Colon Cancer (all estimated with the same Spline model)

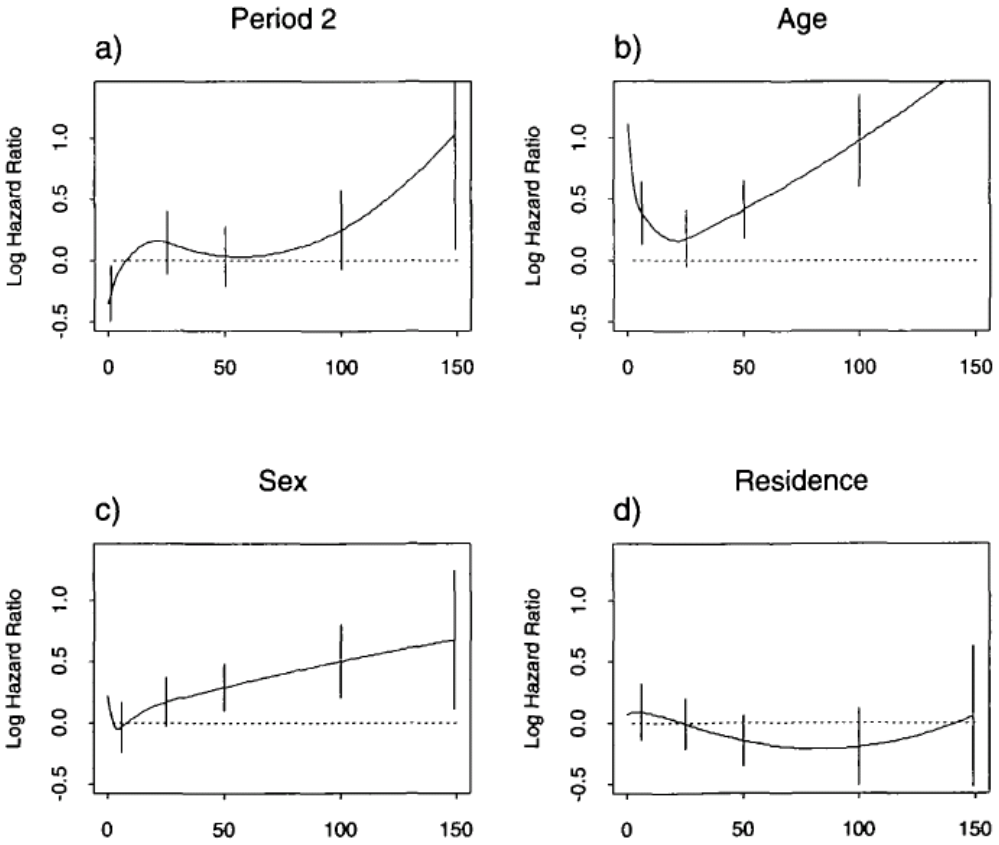


FIGURE 4. Non-parametric 5 d.f. estimates of adjusted time-dependent effects of selected prognostic factors for all-causes mortality in French colon cancer patients. Each panel shows a hazard ratio estimate (solid curve) obtained from the multivariable spline model and the corresponding pointwise 95% confidence intervals (vertical bars) at selected times: a) period 2 (diagnosis in 1982–1986) vs. period 1 (1977–1981); b) age at diagnosis (>65 years vs. <65 years); c) sex (male vs. female); d) residence (rural vs. urban). Horizontal lines correspond to the relative risks of 1.0.

[Quantin, Abrahamowicz, Moreau, et al. *Am J Epi (AJE)* 1999]

TD effect of Karnofsky score (at time 0) vs. Mortality in Advanced Lung Cancer: Initially Low Score is Protective (log HR<0) but the effect disappears by 100 days [Grambsch & Therneau, *Biometrika* 1994]

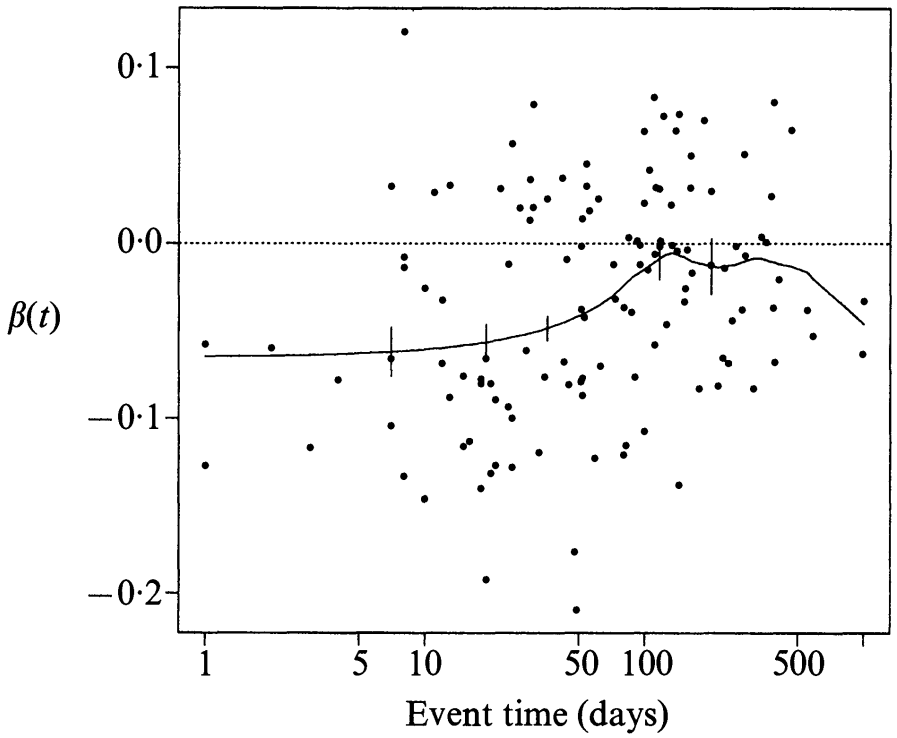
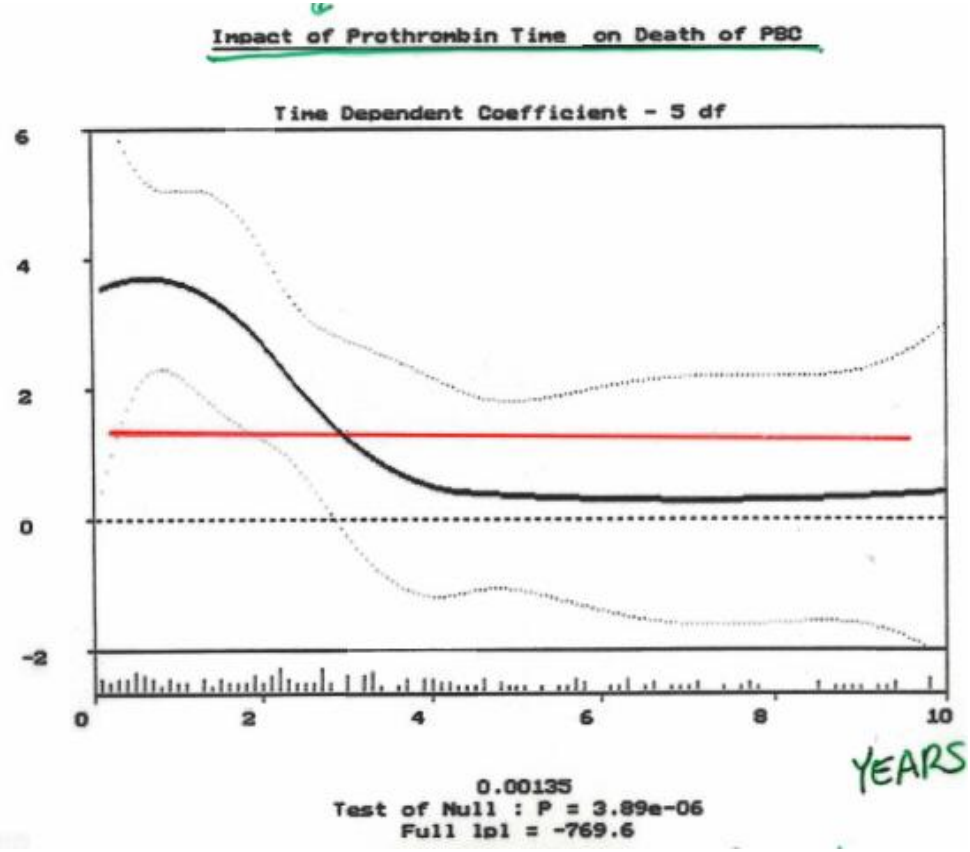


Fig. 4. Scaled Schoenfeld residuals $+\hat{\beta}$ for Karnofsky score plotted against event time from a main effects Cox model fitted to the Veterans data. Average variance standardization is used. A loess smooth (span $=\frac{3}{4}$ and degrees of freedom $= 3{\cdot}7$) is superimposed with 90% pointwise confidence intervals at the 6th, 26th, 46th, 86th and 106th events.

Time-Dependent Effect of a CONTINUOUS variable (Prothrombin time (PT) in PBC)



p=0.03 for the test of time-dependence (TD) refers to the LINEAR effect of PT on the log hazard &, thus, Implies the Slope (HR for 1 unit increase in PT) changes over time

QUESTION: is the underlying LINEARITY ASSUMPTION Valid?

Linearity assumption (re: Effects of Continuous predictors) in Cox PH & Flexible TD models

- **Including an Untransformed CONTINUOUS predictor X in the Conventional PH Cox model imposes (implicitly) the LINEARITY assumption** (common to all General Linear Models):

$$\lambda(t, X) = \lambda_0(t)\exp(\beta X)$$

- In the PH model, Linearity implies the relationship between *X* and the logarithm of the hazard is Linear (with Slope = β)

- Similarly: in flexible TD extensions of the Cox model, Linearity implies that, at any time *t* during follow-up: *the current relationship* between *X* and the logarithm of the hazard is Linear (with Current Slope = β(t))

- **Yet, many important Continuous Risk/Prognostic Factors have highly Non-Linear effects, which are the focus of STRATOS TG2**
  [Sauerbrei et al, *Stat Med* 2014] (overview of the STRATOS initiative)

Extension of the TD model [Abrahamowicz et al, *JASA* 1996] to **Joint flexible modeling of TD & Non-llnear (NL) effects of Continuous predictors** on the hazard

[Abrahamowicz& MacKenzie, *Stat Med* 2007; Wynant & Abrahamowicz, *Stat Med* 2014, 2016]

For a Continuous Predictor X, its joint TD and NL effects are accounted for by modeling log HR(t,x) (HR for value *x*, at time *t*) **as a product of 2 functions**:

$$\log HR(t, x) = \beta(t) r(x)$$

- ***β(t)*** = change over time in the strength of the X's impact on log hazard (**TD effect**)
- ***r(x)*** = shape *(*constant over time) of the Non-linear *risk function*
  i.e. changes in log hazard associated with changes in value of X (**NL effect**)

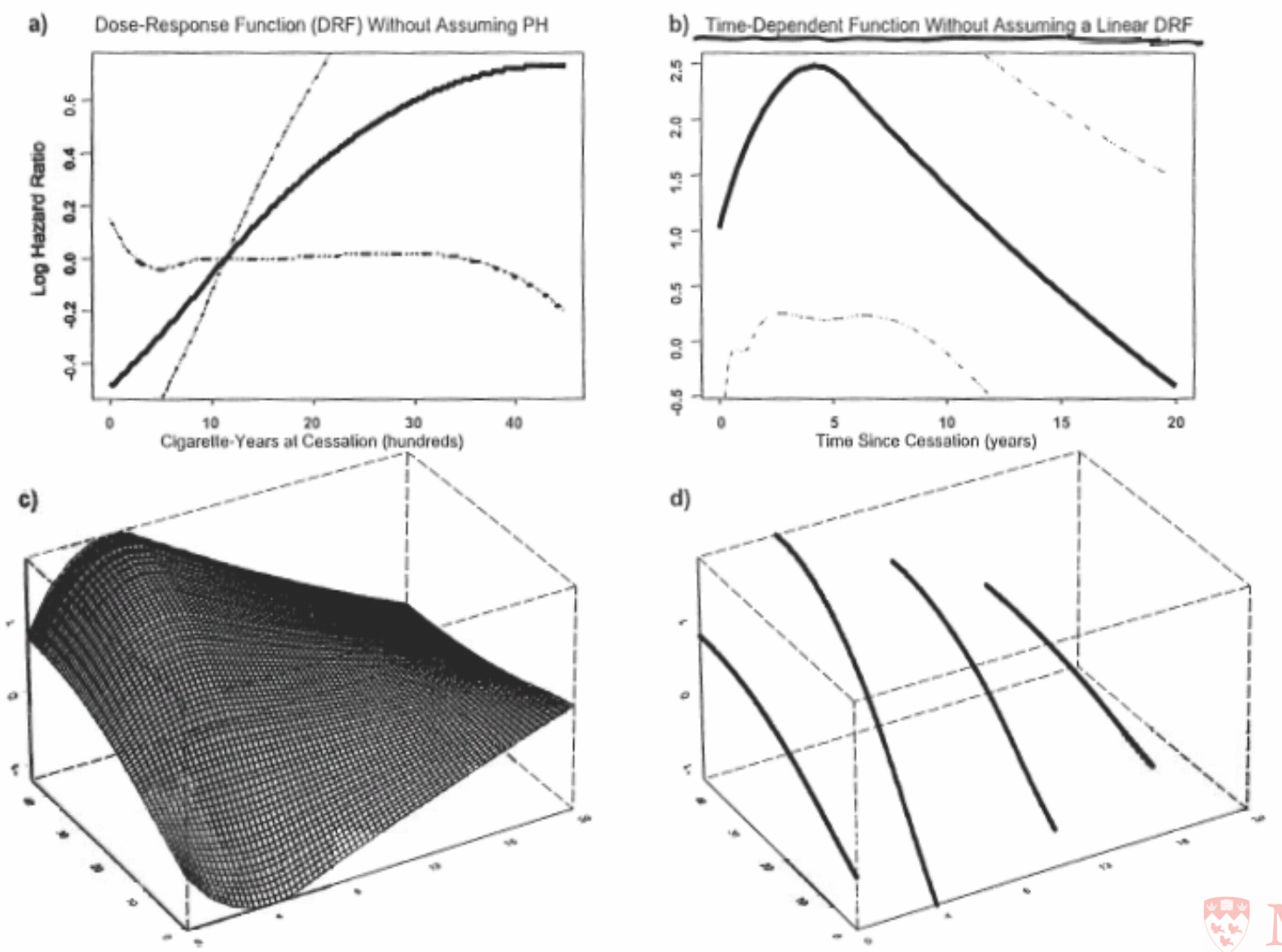
Both β*(t)* and r*(x)* modeled using quadratic regression B-splines

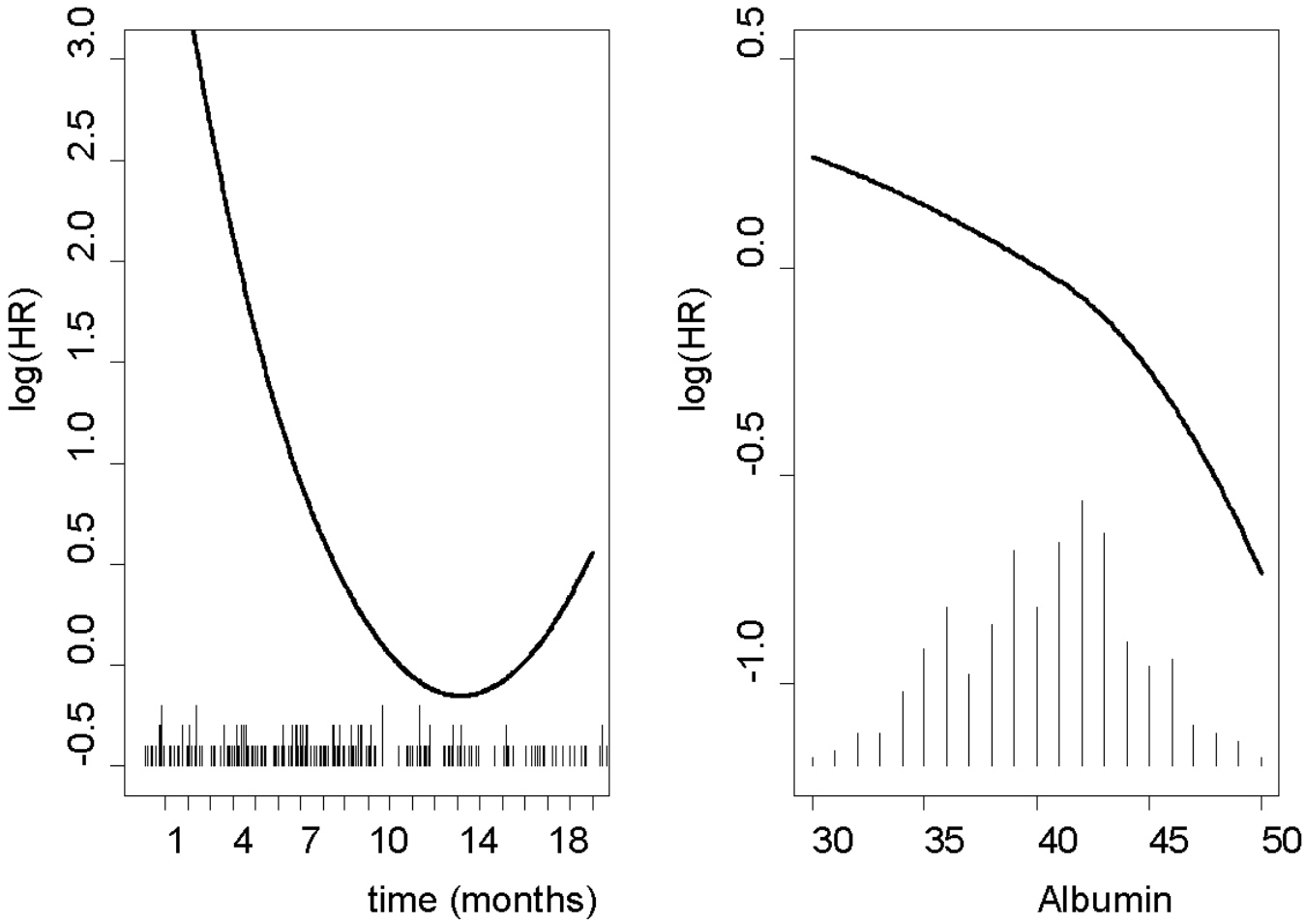
OTHER Flexible TD/NL Models:

- Sauerbrei et al, *Biometrical Journal* 2007 (Fractional polynomials)
- Remontet et al, *Statistics in Medicine* 2007 (Additive NL & TD effects in Relative survival)
- See also comments on the need of consider both NL & TD effects of continuous predictors in Therneau & Grambsch's 2000 book [*Modeling Survival Data*]

NL (top Left) & TD (top Right) effects of **Cumulative Past Smoking Exposure on Lung Cancer** hazard **among Ex-Smokers**

[Abrahamowicz & MacKenzie, *Stat Med* 2007]





Significant TD (left, p<0.001) and NL (right, p=0.024) effects of ALBUMIN on the hazard of Mortality in Non-small Cell Lung Cancer

[Gagnon et al, *Br J Cancer* 2010]

Real-life example of Importance of flexible TD/NL modeling: Albumin is a 'Significant' Predictor for Mortality in non-small cell Lung Cancer Only IF its NL & TD effects are accounted for (p=0.49 in Cox PH/Linear **vs.** p<0.001 in flexible NL/TD models)

Table 3 Results of the multivariable Cox's PH model ($N = 269$)

Variables	HR (95% CI)[a]	*P*-value for test of no association	*P*-value for test of PH	*P*-value for test of linearity
Stage: (IIIB+pleural effusion/4 *vs* IIIA/IIIB)	1.815 (1.268, 2.597)	0.001	0.204	N/A
ECOG[b] performance status: (2 *vs* 0-1)	1.348 (0.958, 1.896)	0.086	0.165	N/A
Smoking status: (ever *vs* never)	2.087 (1.349, 3.230)	0.001	0.135	N/A
Chemotherapy type: (single *vs* double)	1.539 (1.082, 2.188)	0.016	0.067	N/A
Log_2 CRP: (per doubling of CRP values)	1.108 (1.027, 1.196)	0.008	0.039	0.130
Albumin: (per ↓[c] of 1 gl^{-1})	1.015 (0.974, 1.058)	0.485	<0.001	0.024
Log_2 LDH: (per doubling of LDH values)	2.159 (1.700, 2.742)	<0.001	0.636	0.590
Alkaline phosphatase: (per ↑[d] of 10 UI^{-1})	1.019 (0.993, 1.047)	0.150	0.075	0.034
Neutrophil counts: (per ↑ of $1 \times 10^9 l^{-1}$)	1.082 (1.037, 1.129)	<0.001	0.027	0.041
Lymphocytes: (per ↓ of $1 \times 10^9 l^{-1}$)	1.307 (1.050, 1.626)	0.016	0.550	0.460
Deviance[e]	1902.2			
AIC	1922.2			

Abbreviations: AIC = Akaike's information criterion; CRP = C-reactive protein; LDH = lactate dehydrogenase; PH = proportional hazard. N/A: the test of linearity is not applicable to categorical covariates. [a]Adjusted hazard ratio (HR) and 95% confidence interval (95% CI). [b]Eastern cooperative oncology group. [c]↓: decrease. [d]↑: increase. [e]Deviance = −2*log-likelihood.

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Need for Further Extensions to handle Additional Challenges in Survival Analyses

Beyond a Single Endpoint with Exact Event Time (e.g. Death):

- **Competing Risks/Multi-state models** (Multiple Endpoints)**:**
  Andersen PK et al, *Int J Epi* 2012; Andersen PK & Keiding N, *Stat Med* 2012
- **Recurrent Events** (Repeated occurrences of the same event; e.g. stroke)
  Cook RJ & Lawless J, *Stat Methods Med Res* 2002
- **Relative/Net survival** (Disease-specific survival + Unknown death cause)
  Pohar Perme M, Stare J, Esteve J, *Biometrics* 2012
- **Interval-censored data** (Exact event times unknown; e.g. Cancer recurrence)
  Joly P et al, *Stat Med* 2012; Leffondré K et al, *Int J Epidemiol* 2013
- **Joint Modeling of longitudinal marker (e.g. CD4 cells) and event time:**
  Wang Y & Taylor JMG, *J Am Stat Assoc* 2001

Alternative regression models (other than PH & its flexible extensions):

- **Additive Hazards:** Martinussen T, Scheike TH, *Lifetime Data Anal* 2009
- **Accelerated Failure Time (AFT):** Zeng D, Lin DY, *JASA 2007*

Future Steps: Links with other STRATOS Topic Groups

Links Reflected in this talk (but future collaboration needed):

- TG2: *Variables Selection* & *Functional Forms*
  (e.g. modeling NL effects; NL/TD effects vs. variable selection)
- TG6: *Diagnostic & Predictive models*(e.g. predicting Survival)
- TG7: *Causal Inference* (e.g. WCE MSM)

Future Links (to address Challenges Specific to Survival data):

- TG1: *Missing Data*: (for Time-Varying Covariates?)
- TG4: *Measurement Errors* & *Misclassification* (errors in Time-Varying Covariates; Misclassification of Outcomes in Competing Risks; Imprecise Timing of Outcomes (Interval-Censored data); Unknown causes of death (Relative Survival))
- TG5: *Study Design* (Optimal Designs for Time-to-Event studies, Implications for Analysis)?
- *Simulation Panel* (design Complex Time-Varying simulations)
- *Glossary Panel* (establish Consistent Unambiguous Terminology)

CONCLUSIONS

- **Both Time-Varying Covariates & Time-Dependent Effects require careful selection of appropriate Statistical Methods** to Avoid Biased Estimates and/or Incorrect Conclusions
- **Recent, more Flexible Survival Models** are able to address these challenges and **may offer New Insights** into Complex Processes underlying Disease Occurrence, Progression, Treatment and Outcome (that all Evolve over Time)
- However, **Further Challenges need to be addressed** (partly by ***Collaboration with other STRATOS TG's***) **and clear hands-on Guidance for End-users** has to be developed (e.g., re: Software)

THANK YOU, VIELEN DANK

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References (part 1)

- Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. *J Clin Epidemiol* 2006; 59(4): 393–403.
- Abrahamowicz M, Beauchamp ME, Sylvestre M-P. Comparison of alternative models for linking drug exposure with adverse effects. *Stat Med* 2012; 31(11-12): 1014-1030.
- **Abrahamowicz M, MacKenzie T. Joint estimation of time-dependent and non-linear effects of continuous covariates on survival. *Stat Med* 2007; 26(2): 392-408.**
- **Abrahamowicz M, MacKenzie T, Esdaile JM. Time-dependent hazard ratio: modeling and hypothesis testing with application in lupus nephritis. *JASA* 1996; 91(436): 1432-1439.**
- Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012; 41(3): 861-870.
- Andersen PK, Keiding N. Interpretability and importance of functionals in competing risks and multistate models. *Stat Med* 2012; 31(11-12): 1074-1088.
- **Altman DG, De Stavola BL, Love SB, et al. Review of survival analyses in cancer journals. *Br J Cancer* 1995; 72: 511–518.**
- Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. *Rheumatology (Oxford)* 2007; 46: 1157–1160.
- Cook RJ, Lawless J. Analysis of repeated events. *Stat Methods Med Res* 2002; 11(2): 141-166.
- Côté R, Battista RN, Abrahamowicz M, et al. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. *Ann Int Med* 1995; 123(9): 649-655.
- **Cox DR. Regression models and life tables (with discussion). *J R Stat Soc [Ser B]* 1972; 34(2): 187-220.**
- **Dixon WG, Abrahamowicz M, Beauchamp M-E, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012, 71(7), 1128-1133.**
- Franklin J, Lunt M, Bunn D, et al. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with infl ammatory polyarthritis. *Ann Rheum Dis* 2007; 66: 308–312.
- **Gagnon B, Abrahamowicz M, Xiao Y, et al. Flexible modeling improves assessment of prognostic value of C-reactive protein in advanced non-small cell lung cancer. *Br J Cancer* 2010; 102(7): 1113-1122.**

References (part 2)

- **Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; 81: 515–526.**
- Grant S, Chen YQ, May S. Performance of goodness-of-fit tests for the Cox proportional hazards model with time-varying covariates. *Lifetime Data Anal* 2014; 20(3): 355-68.
- Gray RJ. Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. *JASA* 1992; 87(420): 942-951.
- Hastie T, Tibshirani R. Varying-coefficient models (with discussion). *J R Stat Soc [Ser B]* 1993; 55(4): 757-796.
- Hess KR. Assessing time-by-covariate interactions in proportional hazards regression models using cubic spline functions. *Stat Med* 1994; 13(10): 1045-1062.
- Joly P, Gerds TA, Qvist V, Commenges D, Keiding N. Estimating survival of dental fillings on the basis of interval-censored data and multi-state models. *Stat Med* 2012; 31(11-12): 1139-1149.
- Kooperberg C, Stone CJ, Truong YK. Hazard regression. *JASA* 1995; 90(429): 78-94.
- Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2008; 59: 1074–1081.
- Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French hospital database on HIV ANRS cohort CO4. *Arch Intern Med* 2010; 170: 1228–1238.
- Leffondré K, Touraine C, Helmer C, Joly P. Interval-censored time-to-event and competing risk with death: is the illness-death model more accurate than the Cox model? *Int J Epidemiol* 2013; 42(4): 1177-1186.
- McMaster A, Ray DW. Drug insight: selective agonists and antagonists of the glucocorticoid receptor. *Nat Clin Pract Endocrinol Metab* 2008;4:91–101.
- Martinussen T, Scheike TH. The additive hazards model with high-dimensional regressors. *Lifetime Data Anal* 2009; 15(3): 330-342.
- Ng'andu NH. An empirical comparison of statistical tests for assessing the proportional hazards assumption of Cox's model. *Stat Med* 1997; 16(6): 611-626.
- Perneger TV, Abrahamowicz M, Bartlett G, Yerly S. Time-dependence of survival predictions based on markers of HIV disease. Swiss HIV Cohort Study. *J Investigative Medicine* 2000; 48(3): 207-212.

References (part 3)

- Pohar Perme M, Stare J, Esteve J. On estimation in relative survival. *Biometrics* 2012; 68: 113-120.
- **Quantin C, Abrahamowicz M, Moreau T, et al. Variation over time of the effects of prognostic factors in a population based study of colon cancer: Comparison of statistical models. *Am J Epidemiol* 1999; 150(11): 1188-1200.**
- Rachet B, Abrahamowicz M, Sasco AJ, Siemiatycki J. Estimating the distribution of lag in the effect of short-term exposures and interventions: adaptation of a non-parametric regression spline model. *Stat Med* 2003; 22(14): 2335-2363.
- Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994; 96: 115–123.
- Sabin C,Worm S, Weber R, et al. Use of Nucleoside Reverse Transcriptase Inhibitors and Risk of Myocardial Infarction in HIV-Infected Patients Enrolled in the D:A:D Study: AMulti-Cohort Collaboration. *Lancet* 2008; 371: 1417–1426.
- **Sauerbrei W, Abrahamowicz M, Altman D, le Saskia, Carpenter J. STRengthening Analytical Thinking for Observational Studies: The STRATOS initiative. *Stat Med* 2014; 33(30): 5413-5432.**
- **Sauerbrei W, Royston P, Look M. A new proposal for multivariable modelling of time-varying effects in survival data based on fractional polynomial time-transformation. *Biom J* 2007; 49(3): 453-473.**
- Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 1754–1764.
- Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol* 2008; 35: 387–393.
- **Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol* 2008; 167(4): 492-499.**
- **Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med* 2009; 28(27): 3437-3453.**
- **Sylvestre MP, Huszti E, Hanley JA. Do Oscar winners live longer than less successful peers? A reanalysis of the evidence. *Ann Int Med* 2006; 145(5): 361-363.**
- **Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer: New York, 2000.**
- **Tsoukas CM, Bernard NF, Abrahamowicz M, et al. Effect of splenectomy on slowing human immunodeficiency virus disease progression. *Arch Surgery* 1998; 133(1): 25-31.**
- Verweij PJ, Houwelingen HC. Time-dependent effects of fixed covariates in Cox regression. *Biometrics* 1995; 51(4): 1550-1556.

References (part 4)

- Wang Y, Taylor JMG. Jointly modeling longitudinal and event time data with application to acquired immunodeficiency syndrome. *J Am Stat Assoc* 2001; 96(455): OFT895-905.
- Worm S, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010; 201: 318–330.
- **Wynant W, Abrahamowicz M. Flexible estimation of survival curves conditional on non-linear and time-dependent predictor effects. *Stat Med* 2016; 35(4): 553-565.**
- **Wynant W, Abrahamowicz M. Impact of the model-building strategy on inference about nonlinear and time-dependent covariate effects in survival analysis. *Stat Med* 2014; 33(19): 3318-37.**
- **Xiao Y, Abrahamowicz M, Moodie EEM, Weber R, Young J. Flexible marginal structural models for estimating the cumulative effect of a time-dependent treatment on the hazard: reassessing the cardiovascular risks of didanosine treatment in the Swiss HIV cohort study. *JASA* 2014; 109(506): 455-464.**
- **Young J, Xiao Y, Moodie EEM, Abrahamowicz M, et al. Effect of cumulating exposure to abacavir on the risk of cardiovascular disease events in patients from the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr (JAIDS)* 2015; 69(4): 413-21.**
- Zeng D, Lin DY. Efficient estimation for the accelerated failure time model. *JASA 2007; 102(480):1387-1396.*
- **Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005; 162(10): 1016-1023.**
- Zucker DM, Karr AF. Nonparametric survival analysis with time-dependent covariate effects: a penalized partial likelihood approach. *Ann Stat* 1990; 18(1): 329-353.

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User-friendly R SOFTWARE PACKAGES:

- **Therneau T. *survival: A Package for Survival Analysis in S,* version 2.39. R package, 2016, http://CRAN.R-project.org/package=survival.**
- **Sylvestre MP, Beauchamp ME, Kyle RP, Abrahamowicz M. WCE: Weighted Cumulative Exposure Models, version 1.0. R package, 2015, https://CRAN.R-project.org/web/packages/WCE.**