STRATOS & Flexible Modeling of Time-Dependent Covariates in time-to-event analyses

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Focus of STRATOS TG8: TIME = Change

- **STRATOS Topic Group 8 (TG8) focuses on challenges specific to Survival (Time-to-Event) Analyses**
  that usually aim to detect associations 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, Alberta, Canadian Rocky Mts.
site of STRATOS "field study" in July 2016)**

Outline

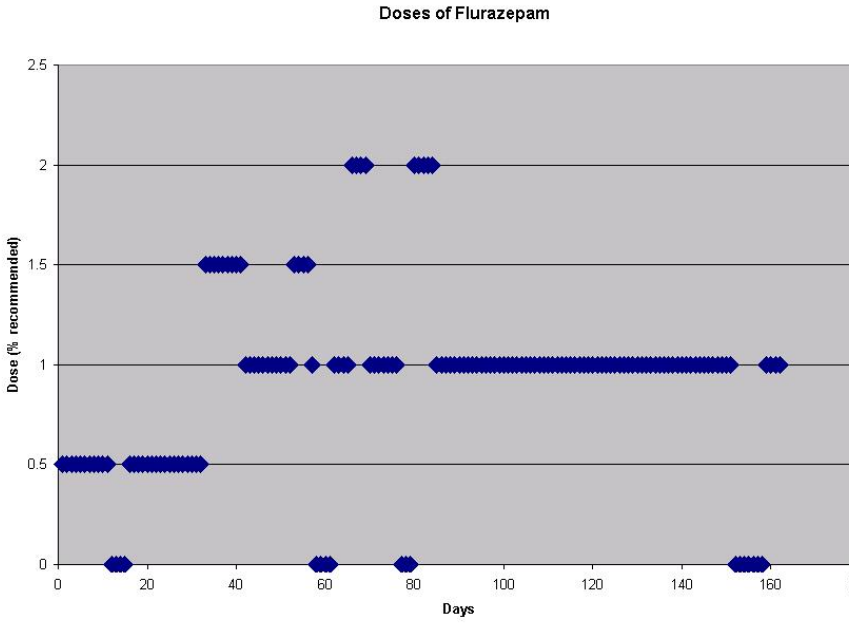
- Survival Analysis has to deal with challenges related to **2 different aspects of Time-related Changes**:
- (1) **Time-Varying Covariates** *** =

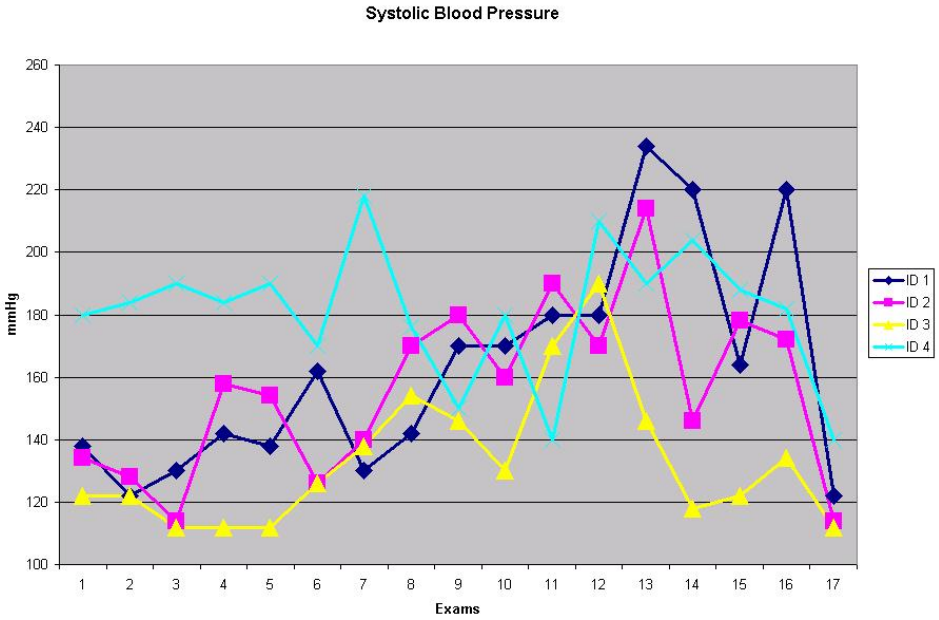
  Changes over Time in the Values or Current status of Predictors
- (2) **Time-Dependent Effects** =

  Changes over Time in the Effects/Associations of Predictors on/with the Hazard for the Event of interest

- *** **I will focus on Modeling of Time-Varying Covariates**:
  (i) outline some **Pitfalls & Analytical Challenges**
  (ii) introduce a **New Flexible Model**
  (iii) illustrate real-life **Applications in Pharmaco-epidemiology**

2 Examples of 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)

Conceptual and Analytical CHALLENGES in Modeling Effects of Complex TIME-DEPENDENT Exposures

- **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)

How Drug Use History is modeled in current Pharmaco-epi studies on Adverse effects of drugs ?

- Most applied Pharmaco-Epi studies define (often *implicitly*) **very simple *Ad Hoc* "Conventional models",** e.g.:

- **Current Use** $M(T) = I\{X(T) > 0\}$
- **Current Dose** $M(T) = X(T)$
- **Any Use in Past N days**:

  $M(T) = I\{X(t) > 0 \text{ for any } (T-N) < t \leq T\}$
- **Total Duration of Past Use:**

  $M(T) = \sum [I\{X(t) > 0\} \text{ for } 0 < t \leq T]$
- **(cumulative) Sum of All Past Doses:**

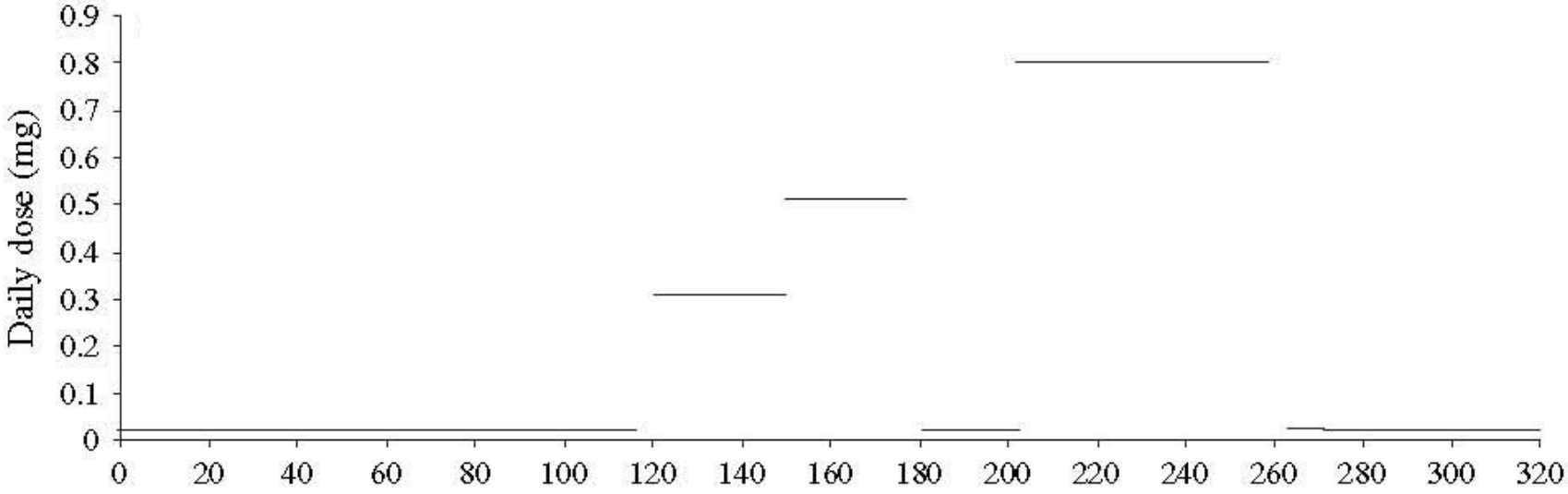
  $M(T) = \sum [X(t) \text{ for } 0 < t \leq T]$

Real-life Example of Arbitrary Definitions of M(T) (Time-Varying drug exposure metric)

- EXAMPLE:
  mutually Incompatible, Arbitrary Definitions of M(T) used in 6 Different Studies [published in top-ranking Rheumatology journals] 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]

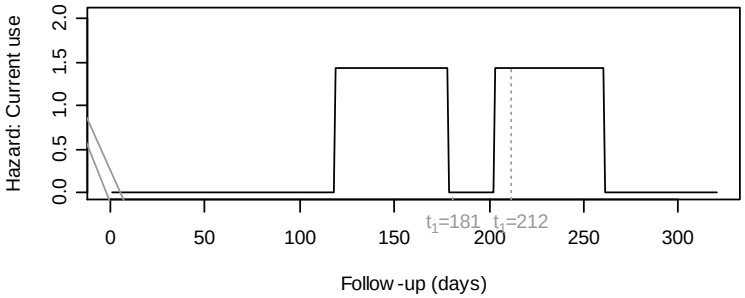
Exposure Pattern (Daily Doses on Y axis) over 320 days of follow-up (X axis) used to illustrate Implications of using Different M(T) metrics (on the Next Slide)

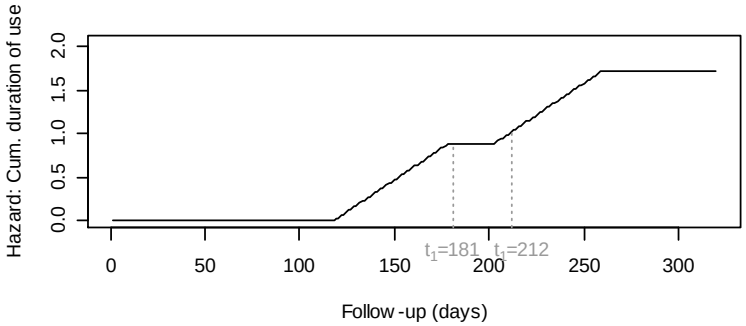


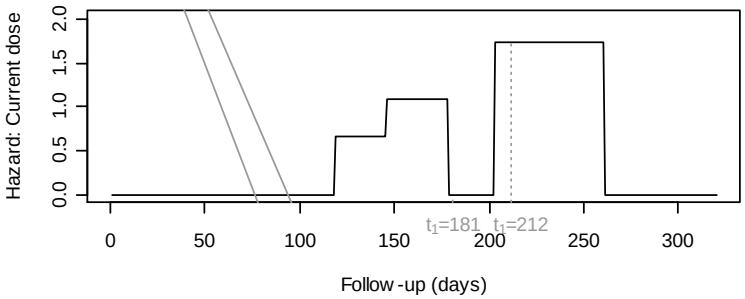
HR's associated with different M(T)'s **

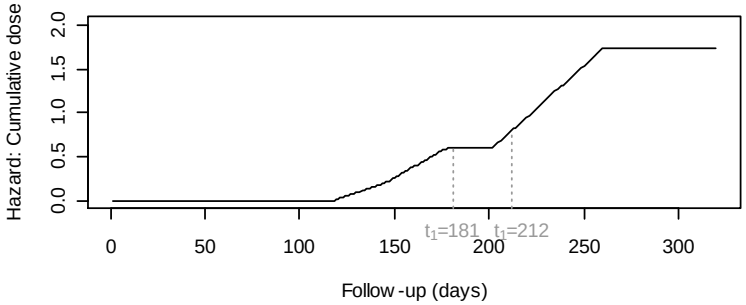
for the SAME Exposure Pattern (shown on Previous Slide) [**

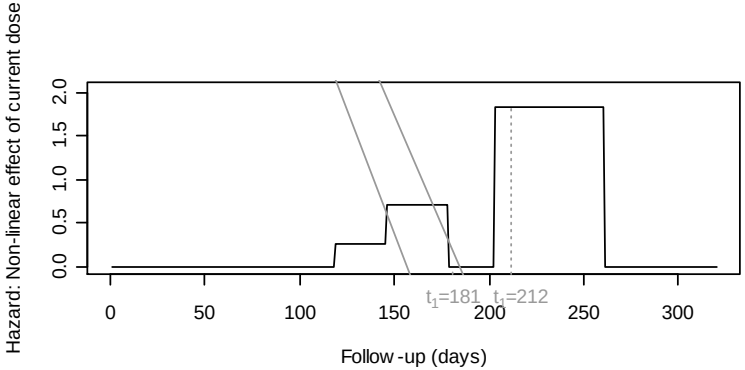
LEFT : **Current Dose/Use vs.** RIGHT: **Cumulative Dose/Exposure Duration**]

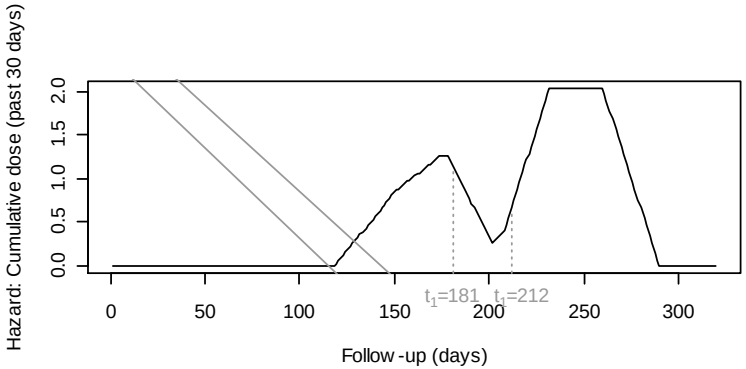












Need to Assess CUMULATIVE Effects

- Our work was motivated by the beliefs that:

(1) **the Effects of Past (Continuous or Intermittent) Use of Medications often Cumulate over Time**

[e.g. Perucca & Gilliam, *Lancet Neurology* 2012, 11: 792=902]

(2) Yet, in real-life studies it is Not clear:

what is the Relative Importance of Exposures that occurred in Different Periods in the Past,

(e.g. 2 days versus 2 months ago) ?

[e.g. Grim et al, *Clinical Pharmacokinetcs 2003, 42: 139-151]*

Weighted Cumulative Exposure (WCE) model

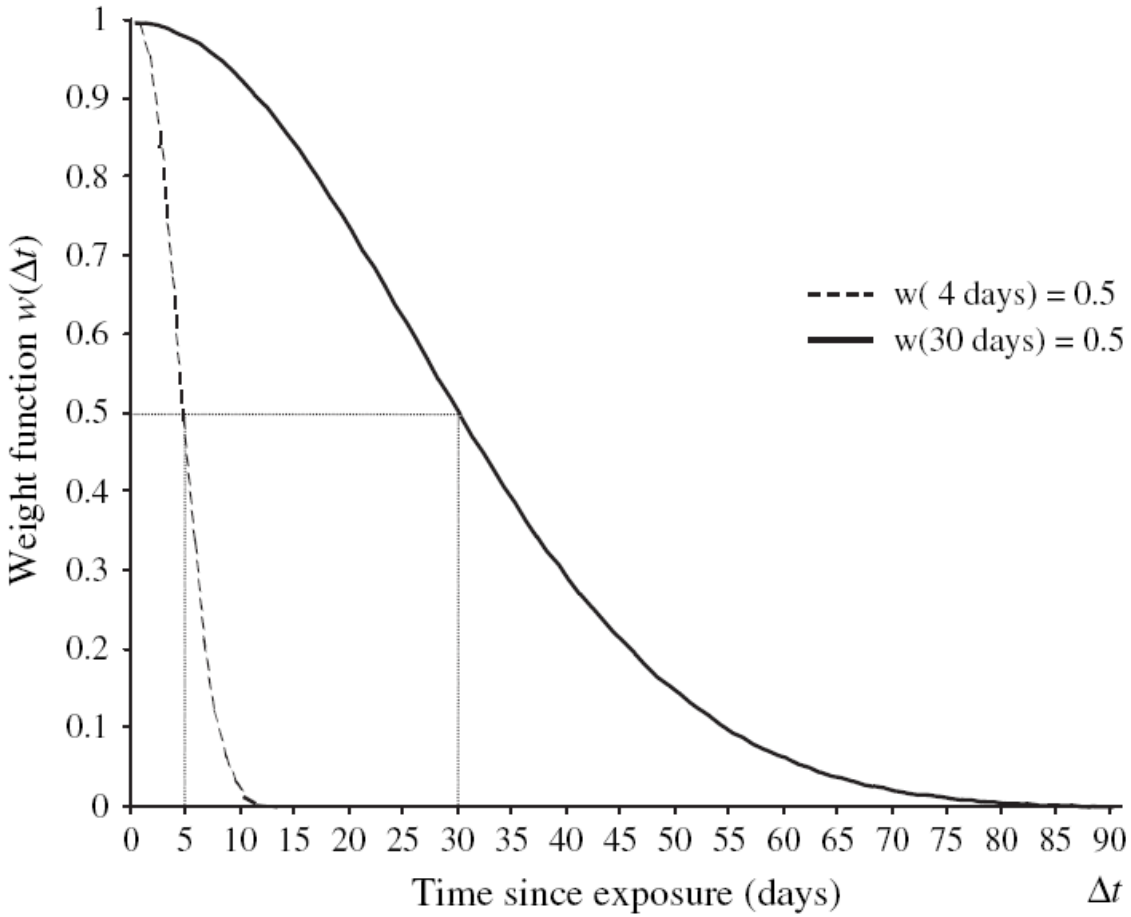
[Abrahamowicz et al, *J Clin Epi* 2006;
Sylvestre & Abrahamowicz, *Stat Med* 2009]

- 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 <u>Weighted Sum of Past Doses:</u>**

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

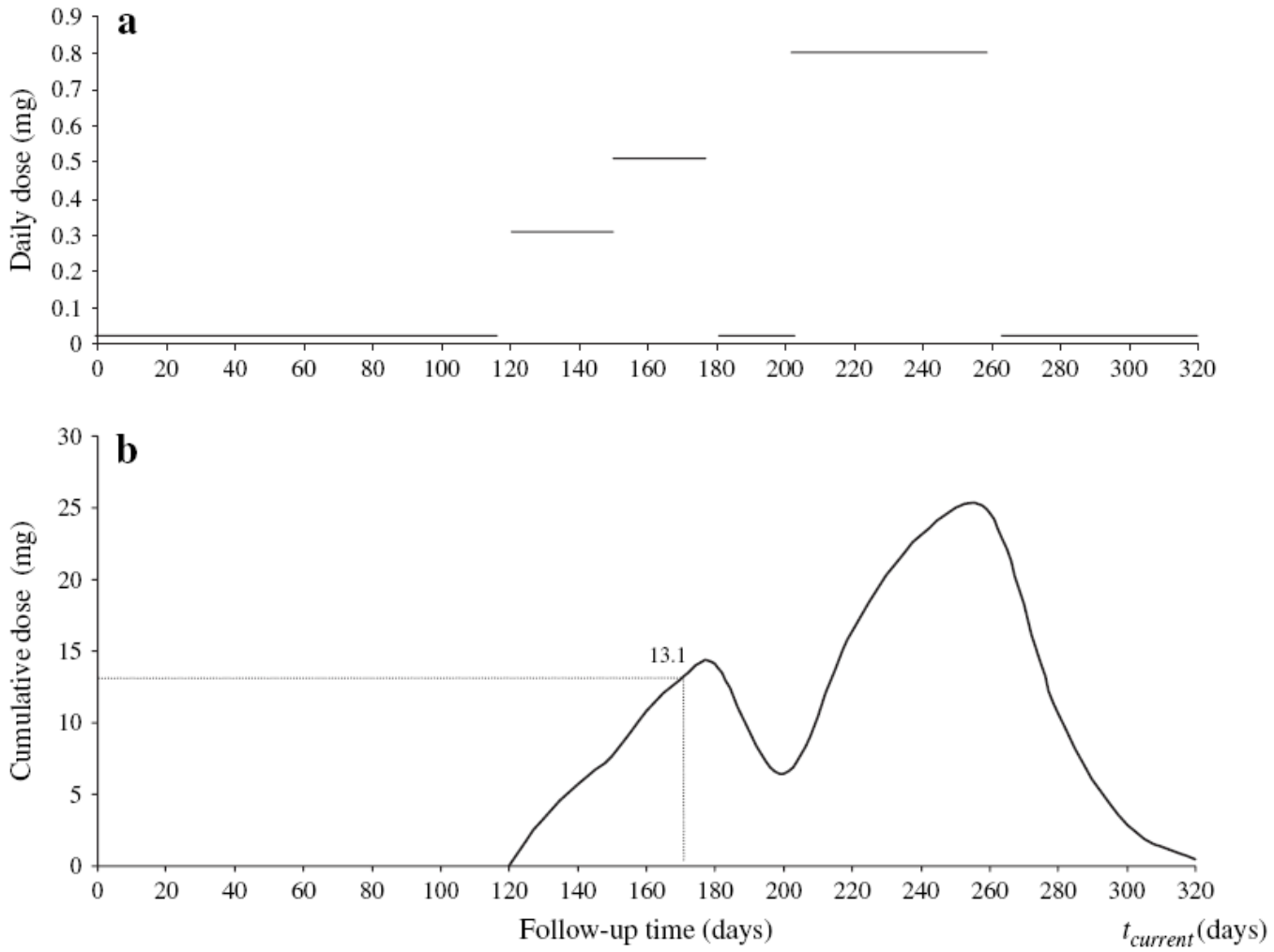
u = current time (when Risk is being assessed)
WCE(u)= Weighted Cumulative Effect of Past Doses (Time-Varying)
X(t) = *D*ose at time *t* ($t \le u$)
u-t = *T*ime elapsed since Dose *X(t)* was received
***w(u-t)* = Weight Function (describing Relative Importance of Dose *X(t)* as a function of Time Elapsed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

Example of a Weight Function



From Abrahamowicz et al, *J Clin Epidemiol* 2006 (Figure 1)

Variation over Time of Dose X(t) [Upper graph]
& the resulting *WCE(u)* calculated using
the Weight Function *w(u-t)* shown on the Previous Slide [Lower graph])



From Abrahamowicz et al, *J Clin Epidemiol* 2006 (Figure 2)

Flexible Spline-based WCE Model

[Sylvestre & Abrahamowicz (*SIM* 2009)]

- To avoid the need to specify its shape *a priori,*
  the Weight function is estimated by Cubic B-Splines:

$$w(u-t) = \sum_{j=1}^{m} \theta_j B_j(u-t) \qquad (2)$$

- Spline Basis is defined over a Limited Support Interval *[0; a]* where:

a = (user-specified) maximum length of the 'etiologically relevant exposure time window'

[Past Doses *X(t)* at *t<u-a* are *a priori* considered irrelevant for the risk at time *u,* implying weight=0]

- We consider also a Constrained model with *w(u-a) = w'(u-a)* = 0, which imposes constraints on 2 last coefficients in (2): $\theta_{(k+4)}=0$ & $\theta_{(k+3)}=0$

ESTIMATION of the Flexible WCE Model through **Artificial Time-varying Covariates**

Then, the resulting Cox's model can be written as:

$$h(u \mid \boldsymbol{X}(u), Z(u)) = h_0(u) \exp\left[\sum_{j=1}^{m} \gamma_j D_j(u) + \sum_{s=1}^{q} \eta_s Z_s(u) \right]$$

Once $D_j(u)$, $j=1,\ldots m$, are calculated
(for each u = un-censored event time),
the above model
can be implemented using standard software
for Cox's model with time-dependent covariates

- the **Program in R** is available on CRAN:
  http://cran.rproject.org/web/packages/WCE

Model Selection

- **We fit models with *k*=1, 2 or 3 'interior knots'** (Uniformly Distributed within *[0; a]* support interval)
- (in addition, 4 'exterior knots' are placed at both u=0 and u=a)
- The resulting Cubic Spline has, respectively, 5, 6 or 7 functional segments, i.e. model (6) [slide 21] requires **estimating *k+4* = 5-7 coefficients θ_j**
- In some applications, the users may also want to consider **Sensitivity Analyses with respect to *a***

  (= the Upper Limit of the Support Interval *[0; a])*

* ***BIC or AIC are* used to select the Best-fitting of the Spline Models with Different (i) *k*** *and/or* **(ii) *a,*** *and/or* **(iii) *constraints***

Simulations Results: True *w(u-t)* (white) vs 100 Un-constrained Estimates [*a*=180 days]

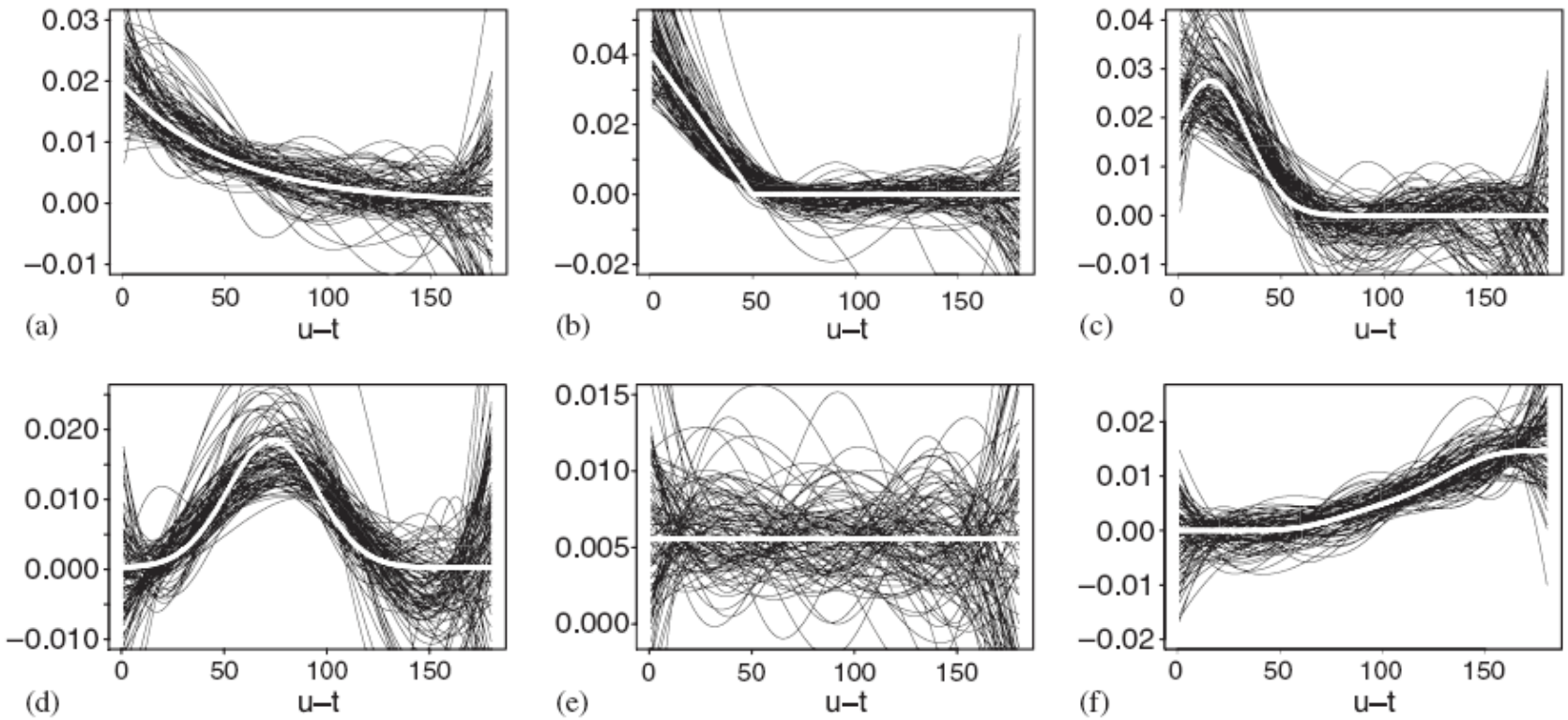


Figure 1. A random sample of 100 normalized estimated weight functions for the unconstrained models with the true weight function in thick white: (a) exponential; (b) bi-linear; (c) early peak; (d) inverted U; (e) constant; and (f) hat. Note that, to make the label of the X-axis readable, we show time in days, while in the text, we use 1 year as the unit of time, so that the values on the axes should be divided by 365.

From Sylvestre and Abrahamowicz (2009, Statistics in Medicine, Figure 1)

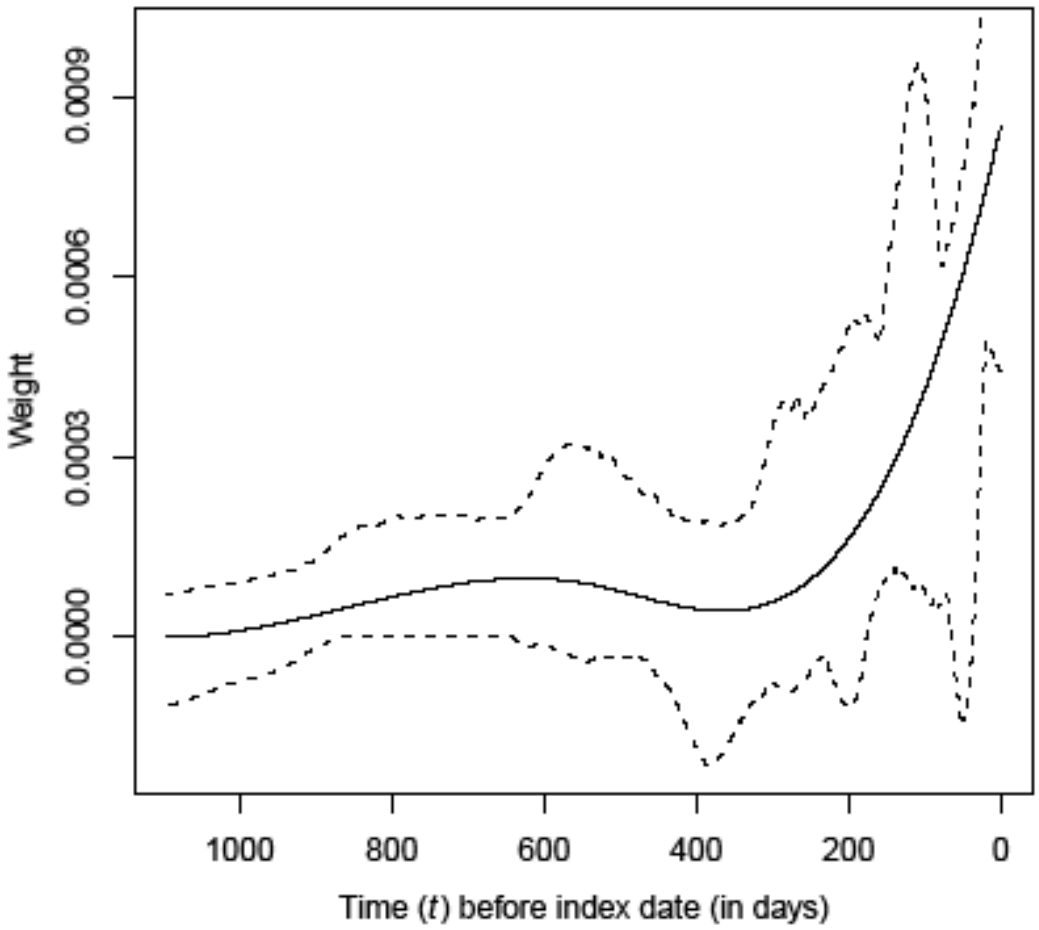
Example of Application of WCE: use of oral Glucocorticoids (GC) vs. risk of serious Infection in rheumatoid arthritis (RA)

- Objective: To explore **if and 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 et al**, ***Ann Rheum Diseases (ARD)*** **2012**]

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: among "Current Users" **Odds Ratios** for Infection **vary considerably depending on the GC Treatment Dose and Duration**

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)**

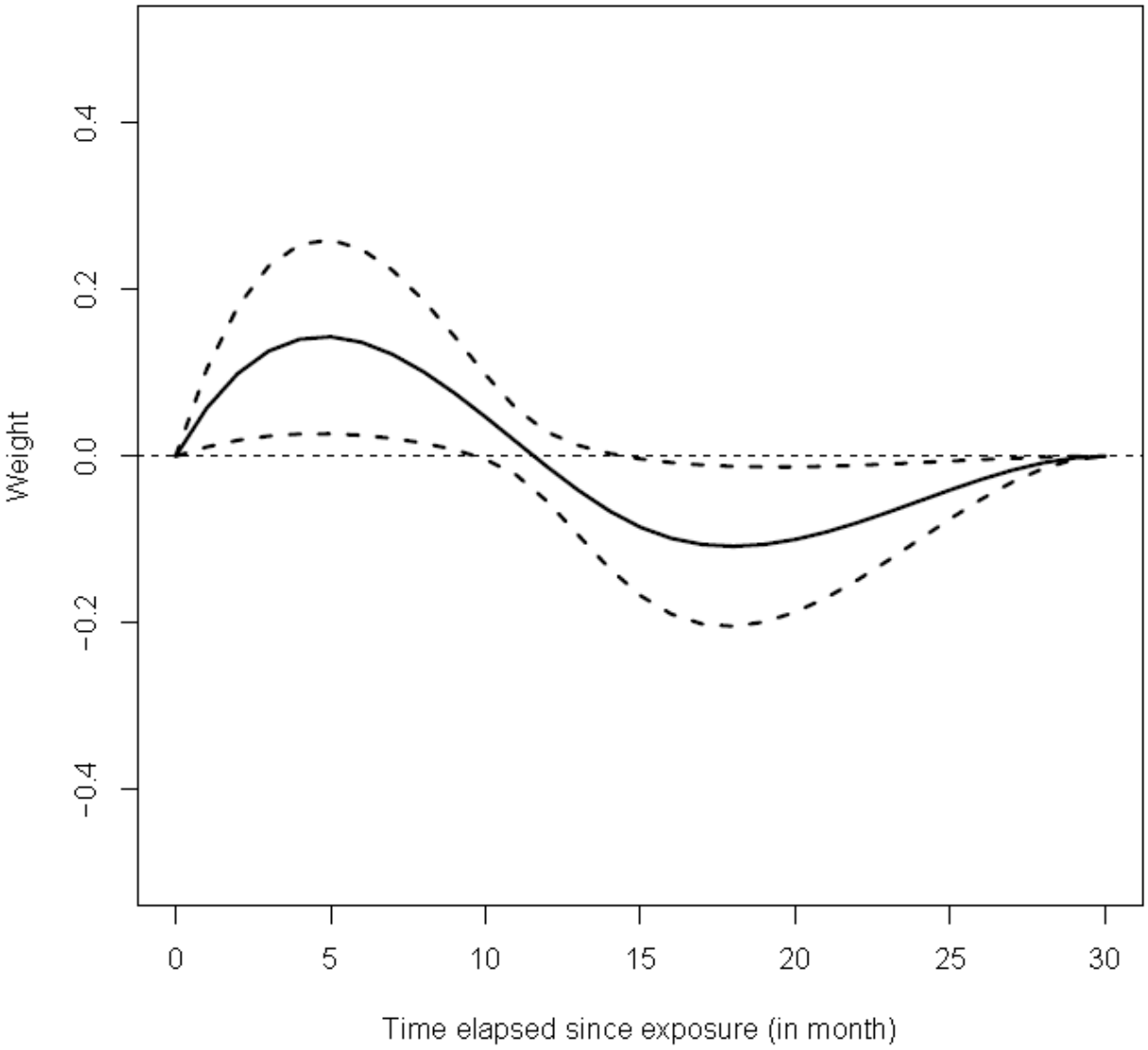
* Odds Ratio for the relative 'risk' of infection for the pattern of use in the 1st column compared to the reference pattern of use in the 2nd column.

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

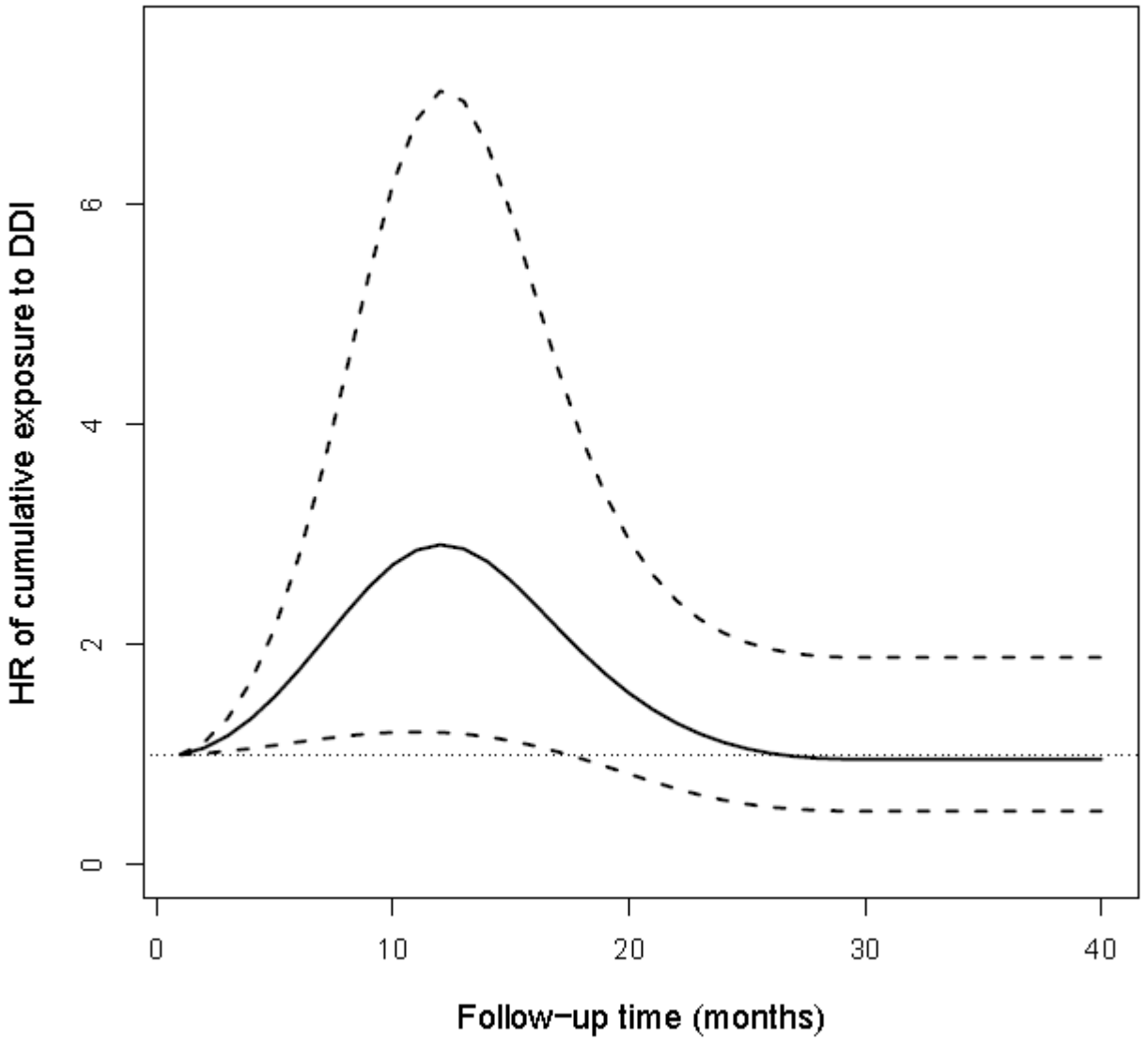
- **Background:** **Inconsistent recent results** [Lang et al, *Arch Int Med* 2010; Worm et al, *J Infect Dis* 2010] re: potential **Increased Cardiovascular (CVD) Risks** with use of **Didanosine (DDI)** (an Nucleoside Analog Reverse Transcriptase Inhibitor (NRTI)) [**Sabin et al, *Lancet* 2008**].
- **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**)



Need for Further Extensions to handle Additional Challenges in Survival Analyses (addressed by STRATOS TG8 members)

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 & Panels

‘Direct’ Links (future collaborations needed):

- TG2: *Variables Selection* & *Functional Forms*
  (criteria for selecting TD covariates, impact of their modeling ?)
- TG6: *Diagnostic & Predictive models* (**Dynamic Prediction of Survival conditional on Updated Time-Dependent covariates**)
- TG7: ***Causal Inference*** (e.g. **extension of WCE to MSM’s**)

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

- TG1: *Missing Data*: (for Time-Varying Covariates?)
- **TG4: *Measurement Errors* & *Misclassification*** (**Exposure Measurement Errors, due to Treatment Non-Adherence in studies of Time-Varying Drug Exposures**)
- TG5: *Study Design* (Optimal Designs for Time-to-Event studies, Implications for Analysis) ?
- *Simulation Panel* (design Complex Time-Varying simulations)
- *Glossary Panel* (establish Consistent Terminology)

CONCLUSIONS

- **Modeling of Time-Dependent Covariates requires careful selection of appropriate "exposure metric'**
- **Flexible Survival Models** are able to address these challenges and **may offer New Insights** into Complex Processes underlying the associations of past and current Treatment with the Hazard of the event of interest
- 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 EFHARISTO

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Selected References

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- 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.

- **WCE Software package:**
- **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.**