Phases of development of Weighted Cumulative Exposure modeling

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STRATOS INITIATIVE

McGill

Goal of Weighted Cumulative Exposure (WCE) modeling

To Assess

CUMULATIVE Effects of Past Values of

Time-Varying Exposures

on the current Hazard in Time-to-Event analyses

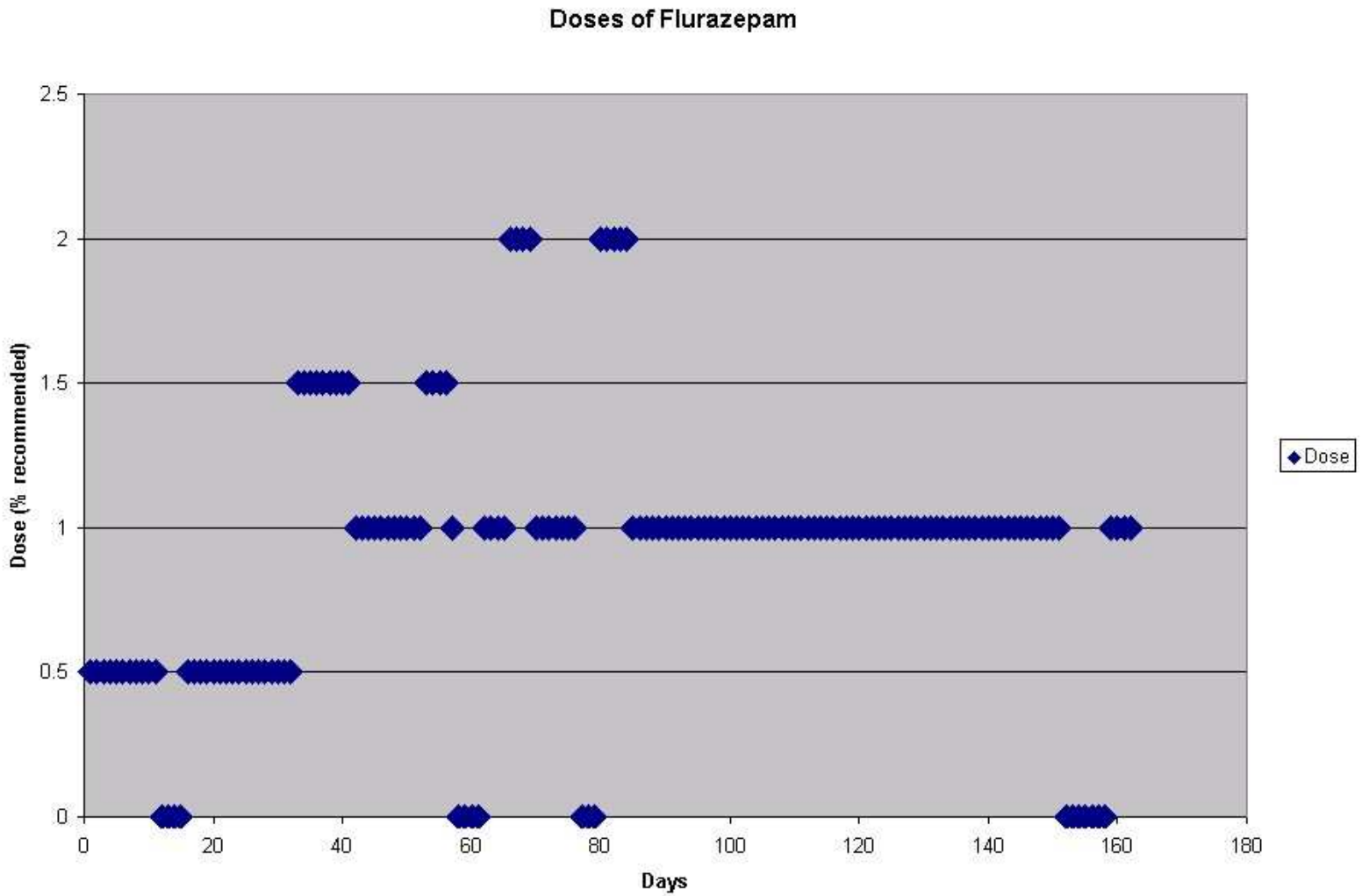
(focusing mainly on **observational**

Pharmaco-epidemiological studies of

Safety or Effectiveness of Medications)

“Phase 0”: Look at relevant **Real-World Data**
example of a Time-Varying Drug Exposure:

6-months Variations of DAILY DOSE of a Psychotropic Drug (Flurazepam) for a Single Elderly Patient



Phase "I A": Identify the **Methodological Challenge**

- **Challenge in Modeling Time-Varying Exposures (TVE):**
  how **to Assess 'current' Relative Risk (e.g. HR) at time *u***
  as **a Function of the History of Past Values** [$X(t)$ for $0 < t \leq u$]:
  HR [u | $X(1), X(2),\ldots X(T\text{-}1), X(u)$] ?

- **Needs a 2-Step Solution:**

  1. **Define Time-Varying aggregate covariate *M(u)*** representing
     Current Value of an **'Etiologically Correct Exposure Metric'**:
     $M(u) = f\,[X(1), X(2),\ldots X(u\text{-}1), X(u)]$

  2. **Use appropriate regression methods** (e.g., Cox PH model for time-to-event analyses) to
     Estimate HR associated with *M(u)*

Phase “I B”:
Identify the **NEED for NEW METHOD(s)**

- Most Pharmaco-Epi studies rely on **Arbitrarily chosen,**
  very simple *Ad Hoc* “Conventional” Time-Varying Exposure Metrics

*** <u>EXAMPLE</u>** of Alternative (formally Incompatible!), Arbitrarily chosen Time-Varying Exposure metrics used in published studies of the Same Association (**Glucocorticoids** use **vs.** risk of **Infections** in Rheumatoid Arthritis):

- ‘*Current* use’ (Binary)
- ‘*Recent* use’ (Binary: Any use in *last month* or last *3 months* or last *9 months*)
- ‘*Ever* use’ (Binary: Use at least once during the *entire past follow-up*, **often many yrs!**)
- ‘Total past dose’ (Continuous, weakly *Monotone Increasing*)

[Franklin J et al, *Ann Rheum Dis* 2007; Lacaille D et al, *Arthritis Rheum* 2008; Smitten AK et al, *J Rheumatol* 2008; Schneeweiss S et al, *Arthritis Rheum* 2007; Bernatsky S et al, *Rheumatology (Oxford)* 2007; Saag KG et al, *Am J Med* 1994]

Phase "I B": (*cont-d*)
Identify the **NEED for NEW METHOD(s)**

- Need to accurately **assess Cumulative Effects of past Drug Use**
  [Pazzagli et al, *Pharmacoepidemiol Drug Saf* 2018; WHO, *Organ Tech Rep Series* 1972; Abrahamowicz & Tamblyn, *Enc Biost* 2005]

- **Risks** (and benefits) of using a specific drug likely **depend on** the treatment's: **(i) dose, (ii) duration and/or (iii) its recency** **
  [Edwards & Aronson, *Lancet* 2000; Perucca & Gilliam, *Lancet Neurol* 2012]

** **This implies that conventional Cumulative Dose (Sum of all past doses) or Cumulative Duration of Use may NOT be accurate TVE Metrics!**

Phase "I C": Concept & Formulation of the New **Weighted Cumulative Exposure (WCE) Model**

$$WCE(u) = \sum_{t \le u} w(u-t) * X(t) \quad (1)$$

u = current time (when Risk is being assessed)

$WCE(u)$ = Weighted **Cumulative Effect** of the Past Exposures on hazard at time u

$X(t)$ = exposure intensity (**dose**) at time t ($t \le u$)

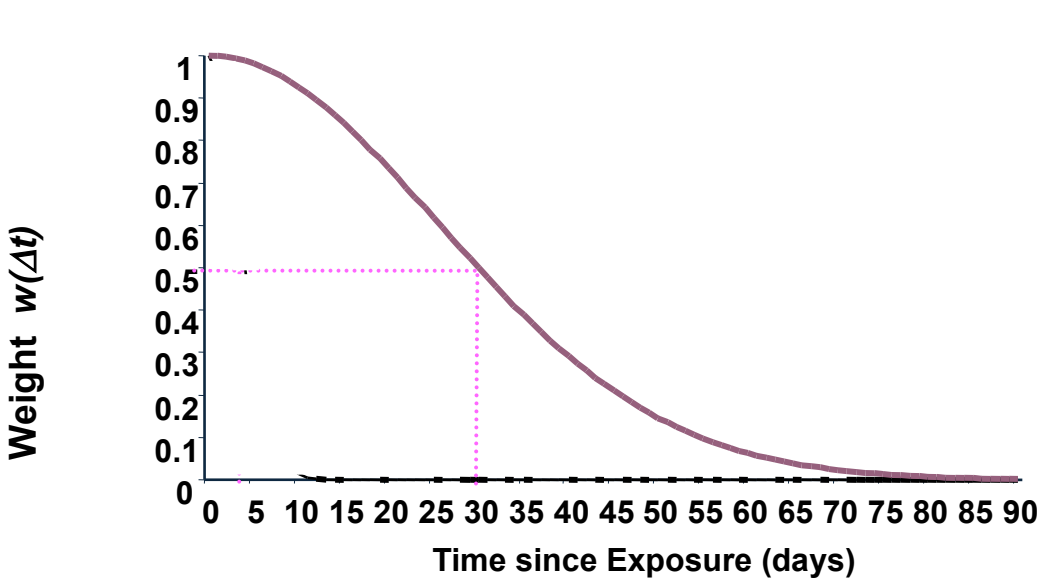
u-t = **time** elapsed since exposure $X(t)$

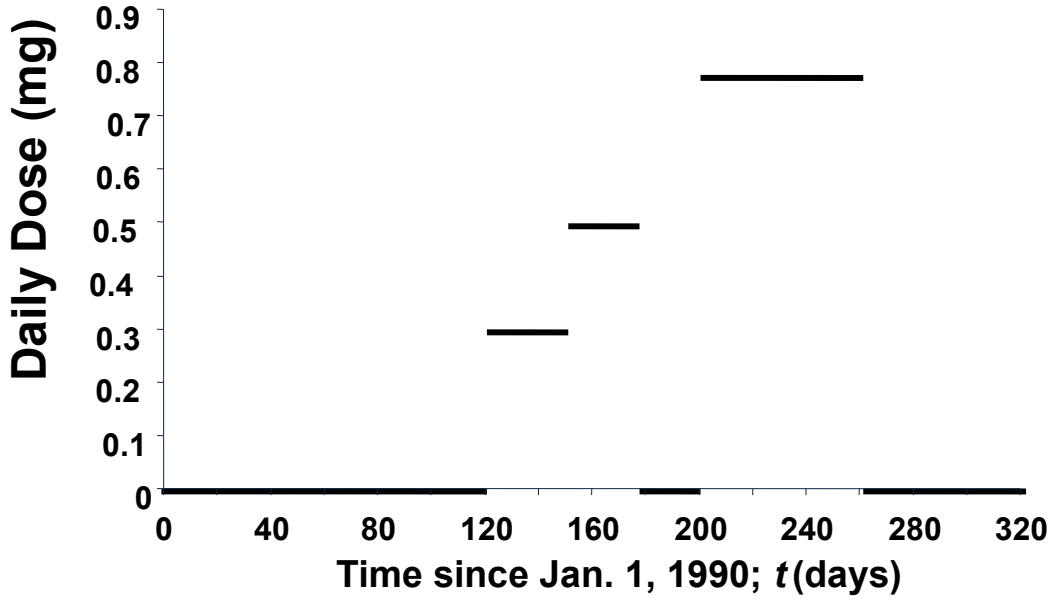
$w(u-t)$ = **Weight function**, estimates Relative Importance assigned to exposure $X(t)$ as a function of Time-since-Exposure *(u-t)*

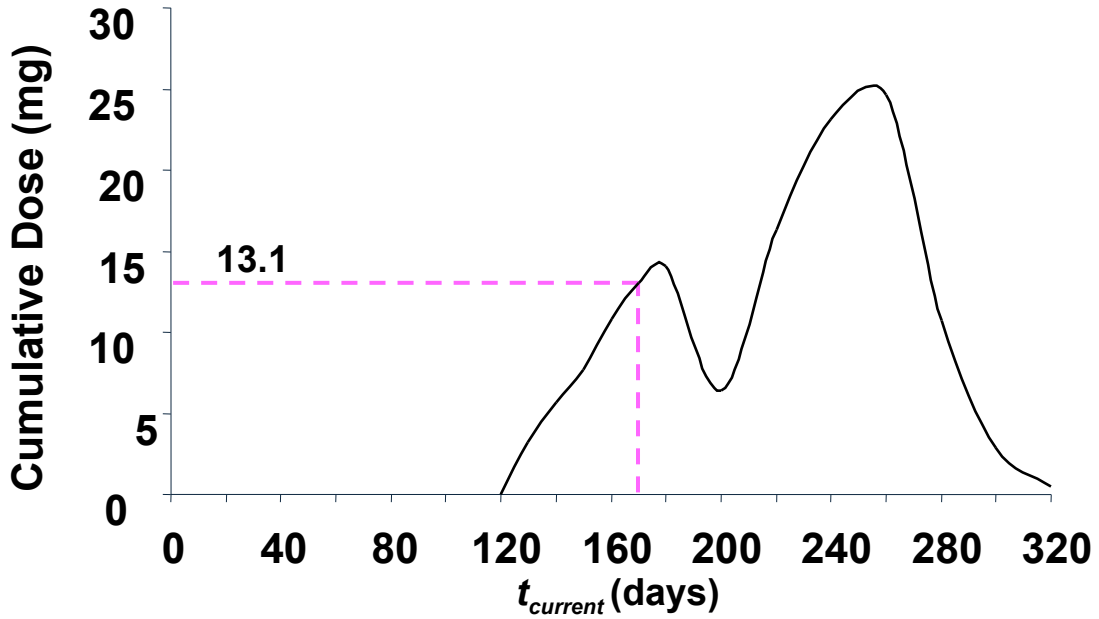
***WCE*(*u*) is then included as a Time-Varying Exposure metric in, e.g., Cox model for time-to-event analyses**

[Sylvestre & Abrahamowicz, *Stat Med* 2009]

Weights for Cumulative Exposure







Phase "I D": Proof of the Concept

- To demonstrate the **practical usefulness of the WCE concept**, in the 1st WCE paper we applied the weight function (shown on slide 8), selected *a priori* based on known pharmaco-dynamics of the drug, in a **real-world pharmaco-epi database** [Tamblyn et al, *J Am Geriatr Soc* 2005]

- The goals were to (i) re-assess the **association between recent use of Temazepam (a psychotropic drug) and hazard of fall-related injuries** (presumably partly due to drug-induced cognitive impairment), and (ii) compare the fit (AIC) of the WCE model with simpler 'conventional' exposure models [Abrahamowicz et al, *J Clin Epidemiol* 2006]

  N = 3,798 new Temazepam users,
  follow-up: max = 5 yrs, median = 2 yrs, **186 Events** (falls) (4.9%)

  WCE model fit much better than any of the 5 conventional models, with 7.5 points improvement in AIC !

  Best-fitting WCE model for (weighted) Cumulative Duration, adjusted for current dose:
  AIC = **2262.4 *versus* 2269.8** for the Best-fitting Conventional model (Un-weigthed Cumulative Duration) [Abrahamowicz et al, *J Clin Epidemiol* 2006]

Phase "I E": Refined **Estimation** (Flexible modeling)

- In most real-life applications, the relative importance of doses taken, e.g., 1 week ago vs. 3 months ago is difficult to specify *a priori* !
  [Pazzagli, *Pharmacoepidemiol Drug Saf* 2018; Abrahamowicz & Tamblyn, *Enc Biost* 2005]

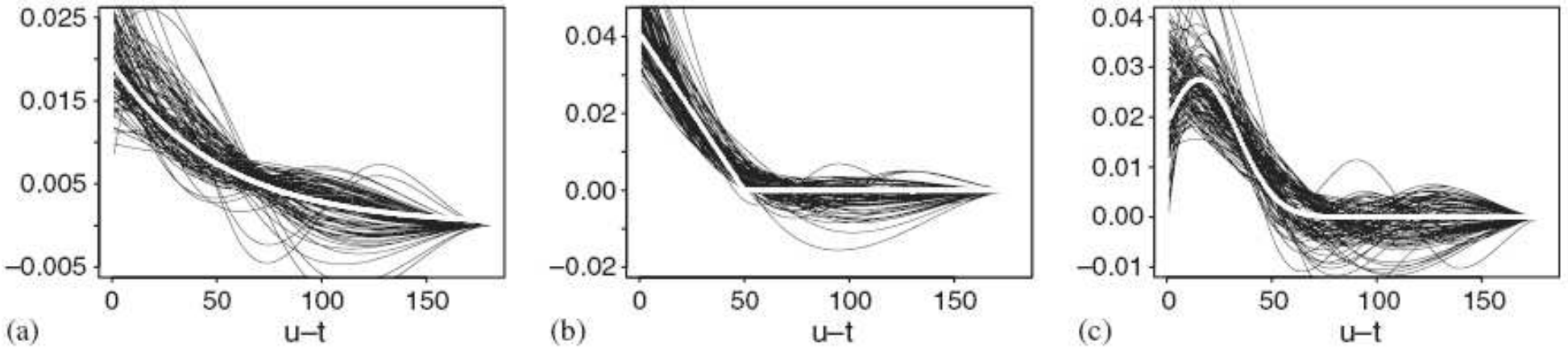
- Thus, in our next WCE paper we model a **flexible Weight function *w*(*u*-*t*) using unpenalized Cubic regression Splines** [Sylvestre & Abrahamowicz, *Stat Med* 2009]:

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

where: B_j, $j=1,\ldots,m$, are the m functions in the Cubic Spline basis, and θ_j are the estimable spline coefficients **

** The model can be fit using ***standard R functions for time-dependent Cox model*** using ***Artificial Time-varying Covariates*** [Sylvestre & Abrahamowicz, *Stat Med* 2009]

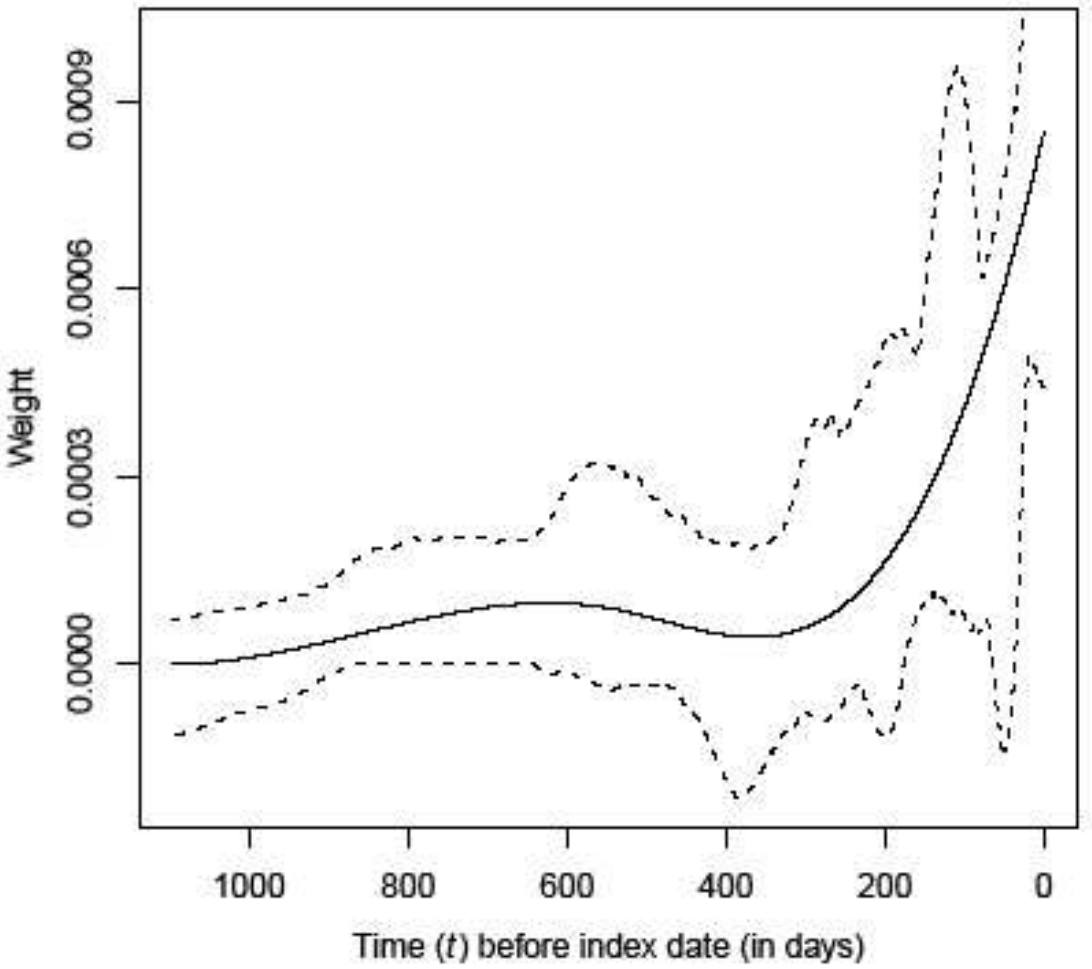
Phase "II A" (Initial Evaluation in Simulations)
Clean Data, 250 events, True model = WCE
[Sylvestre & Abrahamowicz, *Stat Med* 2009]



- **Initial Simulation results:**
  - **Reasonably Unbiased & Stable Weight function Estimates** (only 250 events)
  - Selecting *Time Window that is Too Long has little impact* (Middle & Left panels)
  - Constraining $w(u\text{-}t)$ to fall to 0 at the right end of time window stabilizes estimates

Phase "II B" (Initial "ideal" Application: Large N (>1800 events), strong association

- Dixon et al [*Ann Rheum Dis* 2012] (**395 citations on Google Scholar**)
- Glucocorticoids vs Infection-caused hospitalizations in Rheumatoid Arthritis
- **WCE model had AIC 28 points better than any of 9 conventional models**



Phase "II B": Initial "ideal" Application (cont-d):

New (*plausible/interpretable*) Insights from WCE analyses

- **Current Infection risk is affected by Cumulative effects of GC exposures in past 2-3 years**** (*contrary to previous beliefs that the latency does not exceed 3-6 months…)*

  ****** AIC for best fitting 3-yrs WCE model improved by 34.3 or 8.6 relative to WCE models restricted to 3 m. or 1 yr.** [Dixon et al, *Ann Rheum Dis* 2012]

- **Possible Biological Interpretation of the "Bi-modal effect":**
  - **GC act on both (i) Innate & (ii) Adaptive Immune Systems**
  - (i) Short-Term effect of doses from last 3-6m. on Innate system was known
  - (ii) Long-Term effect on Adaptive system may be Indirect, involving T-lymphocyte apoptosis & failure to generate pathogen-specific adaptive immune responses [McMaster & Ray, *Nat Clin Pract Endocrinol Metab* 2008], or prolonged adrenal suppression

Phase "II/III" (*Re-purposing*): WCE model's **Extensions**:

1) Non-Drug Exposures:

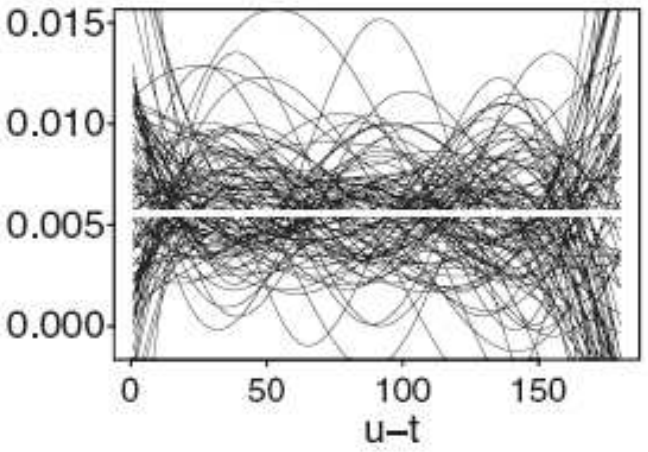
- 1a): $X(t)$ = Radiation doses [Danieli et al, *Am J Epi* 2019];
- 1b): $X(t)$ = Air pollution [Biel et al, *Scientific Reports* 2020]
- 1c): $X(t)$ = Physical activity's intensity [Wang et al, *Paediatr Perinat Epidemiol* 2025]

2) More Complex Models (beyond single-endpoint survival):

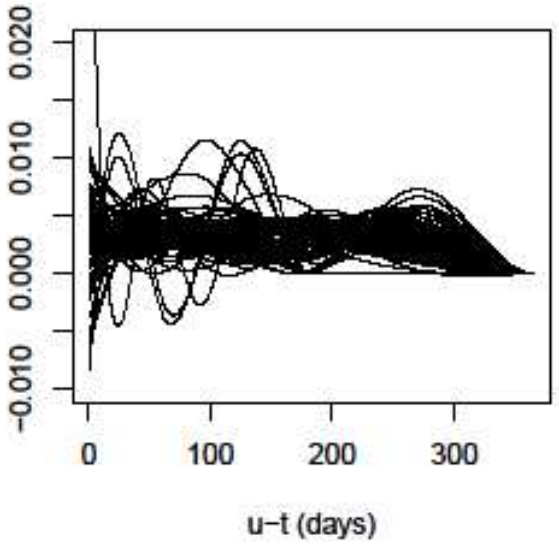
MODEL	Statistical Reference	Methods	Real-world APPLICATION	Applied REFERENCE
Competing Risks	Danieli et al, *SMMR* 2019	Data Augmentation (Separate Weights for Com events)	Radiation vs Cancer OR Other-Causes Mortality	Danieli et al, *Am J Epi (AJE)* 2019
Marginal Structural Cox Models (MSM)	Xiao et al, *JASA* 2014	IPT weights for time-varying confounders	Didanosine vs CVD risks in HIV	Young et al, *J AIDS* 2015
Mixed Effects Linear models	Danieli et al, *SMMR* 2020	Changes in Longitudinal	Opiods vs Changes in the	Bhondoekhan et al

Phase "III": Further Simulations: **Comparing with Simpler Models** + regression **Diagnostics**

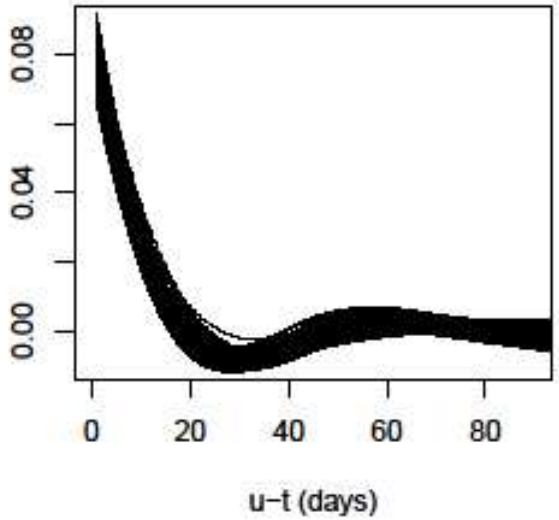
250 events



500 events



500 events



- **Left & Middle graphs: Over-fit Bias** when True model is Simple** (UN-weighted Cumulative Dose)**

  ** **improving if more events** [Sylvestre & Abrahamowicz, *Stat Med* 2009]

  - **Diagnostics: 3-df LRT's p>0.05 for 94% of samples: WCE does NOT improve model's fit to data vs. Un-weighted Sum of Past Doses**

- **Right graph: True model = Current Dose (WCE estimate suggests Very Short-term impact);**

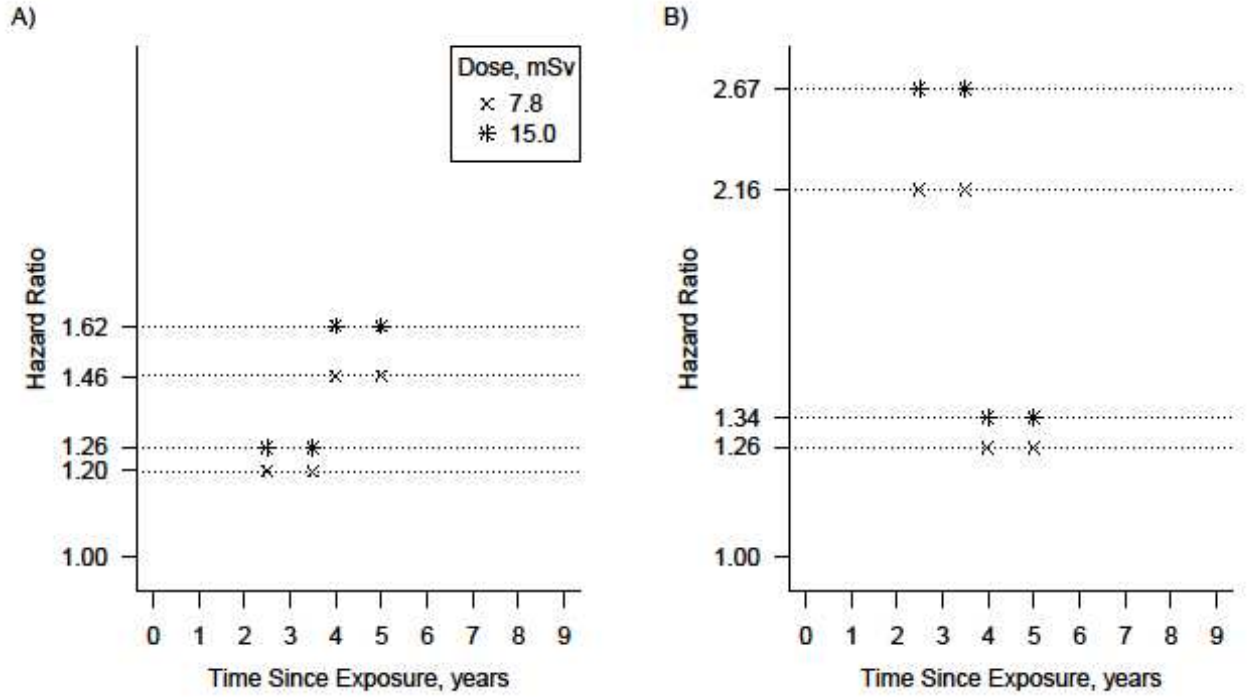
  - **Diagnostics: AIC favors Current Dose over WCE in All samples** [Abrahamowicz et al, *Stat Med* 2012]

Phase "III" (Advanced Applications): **User-friendly presentation** of complex WCE results

WCE-based
Infection ORs for various clinically relevant patterns of GC use
[Dixon et al, *Ann Rheum Dis* 2012]

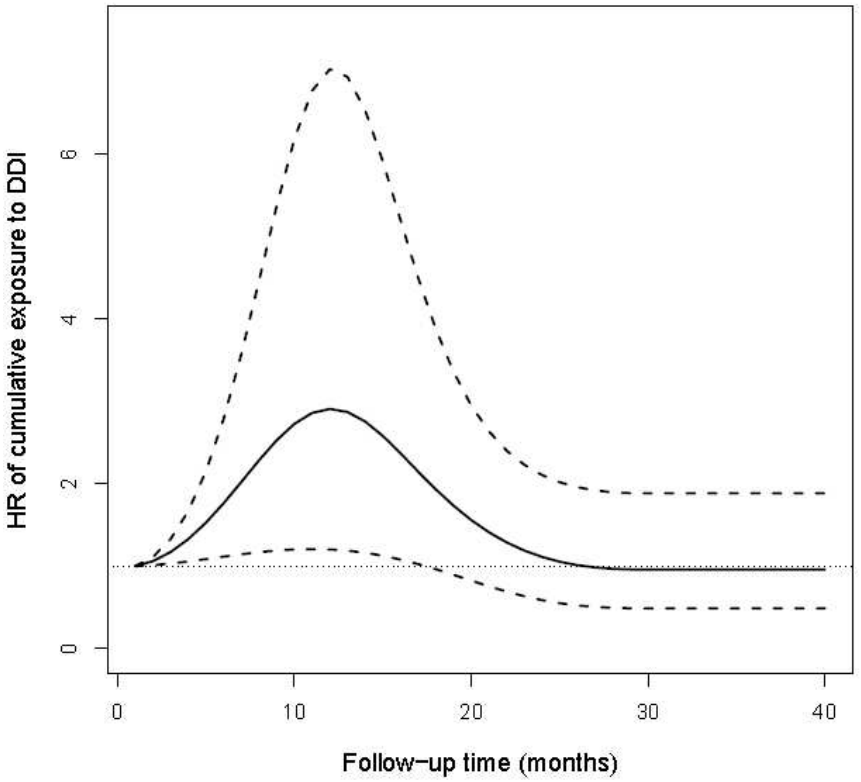
Pattern of use	Reference	OR
Current user, 5mg, for last 28 days	Non-user	1.11 (1.08, 1.26)
Current user, 5mg, for last 3 months	Non-user	1.30 (1.21, 1.45)
Current user, 30mg, for last 28 days	Non-user	1.84 (1.58, 4.00)
Current user, 30mg, for last 3 months	Non-user	4.82 (3.12, 9.29)

Competing-risks WCE **HRs for Cancer incidence for selected real-world patterns of past doses of low-dose ionizing radiation** (LDIR)
for Men (Left) vs. Women (Right)
[Danieli et al, *Am J Epidemiol* 2019]

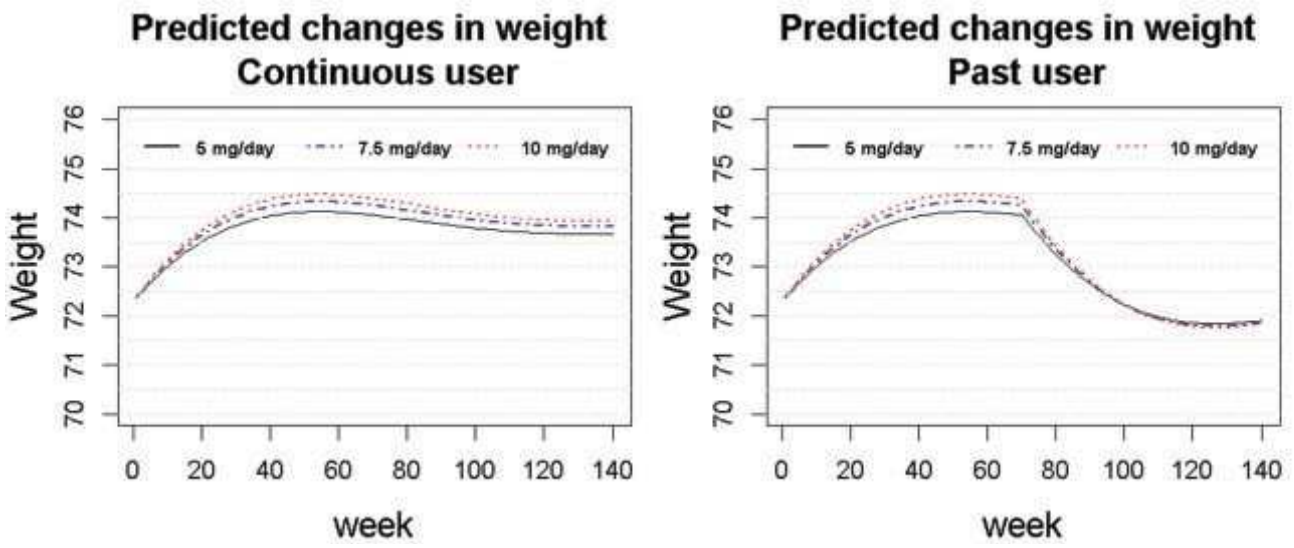


Phase "II and/or III" (Advanced Applications): User-friendly presentation of complex WCE results

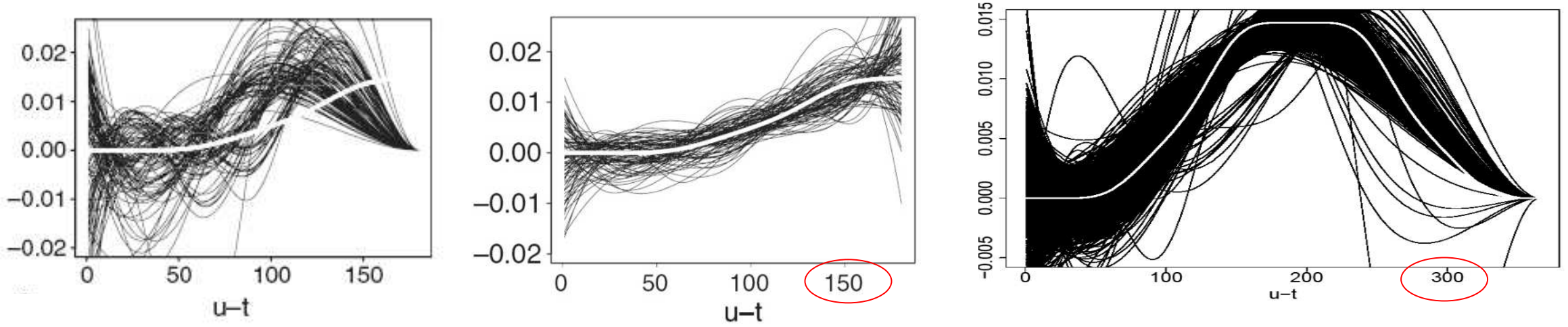
Changes in CVD hazard with Increasing Duration of continuous Didanosine Tx in HIV [Xiao et al, *JASA* 2014]



Changes in the Body Weight for a woman with baseline weight of 72.4 kg, according to different patterns of Glucocortisteroids use
[Danieli et al, *SMMR* 2019]



Phase "III/IV": Advanced Simulations: **Diagnostics** to Identify **Potential Problems in Applications** [Sylvestre & Abrahamowicz, *Stat Med* 2009]



3 *w*(*u-t*) Estimates for True = "Hat" function over 360 days (White curve in Right panel):

1. **Left: Wrong support window (Only 180 days) with *w*(*u-t*) Constrained to 0 at the end**
2. **Middle: 180 d. window But *w*(*u-t*) UN-Constrained (LRT's p < 0.05 in 87% samples) ****
3. **Right: Correct window (360 d.) Best Fit (Minimum AIC in All samples) *****

**** 2-df LRT of Constrained vs. Unconstrained model = DIAGNOSTIC test for Time Window**

***** > 4 points AIC Difference validated in simulations as model choice's criterion**

[Abrahamowicz et al. *Stat Med* 2012]

Phase "IV": Independent Recommendations & Narrative Reviews

- **Review of time-varying drug exposures [Pazzagli et al. *PDS* 2018]:**

  identifies **Cumulative Effects of past Drug Use among 1 the 4 most important challenges**, & **recommend WCE methodology** for such analyses

- A dedicated **Narrative Review [Kelly et al. *PDS* 2024] of WCE modeling in 17 real-world pharmaco-epi studies** concludes:

  - *"The WCE method is an important tool for exploring the effect of time-varying exposures on an outcome, including the dose, duration, and timing of past exposures, … and allows additional insights into their effects."*
  - *"… WCE is a powerful addition to conventional methods of classifying exposure…"*
  - *9 of the 10 papers that compared alternative exposure models reported Best Fit of WCE*

Missing elements of Phase III: Neutral Comparisons

- Still TO DO:

  <u>Neutral Simulation-based Comparisons</u> with

  Alternative flexible Models ** proposed to assess

  Cumulative Effects of Time-Varying Exposures

  (as recommended for Phase III by [Heinze et al. *Biom J* 2024]):

  ** 1/ **Distributed Nonlinear Lags Models (DNLMs)**
  [Gasparini, *Stat Med* 2014; Gasparini et al. *Biometrics* 2017]

  2/ **Exposure-time-response models** [Berhane et al. *Stat Med* 2008]

  <u>CHALLENGE:</u> both 1/ & 2/ use 3D Tensor Product splines

WCE Software (*only in R*)

- **CRAN Webpage** (Comprehensive R Archive Network)
  https://CRAN.R-project.org/package=WCE
  [Sylvestre, Beauchamp, Kyle, Abrahamowicz, *R package* 2024]
- **Detailed Example illustrating package implementation in real-world analyses, based on a dataset included in the package**
  https://cran.r-project.org/web/packages/WCE/vignettes/WCE.pdf
  (Temporarily unavailable, see here for now
  https://github.com/mebeauchamp/WCE-R-package)
- **DOWNLOADS since 2015: >32,000**
- Code for extensions available upon request

Summary & Conclusions

(*Still on-going*…) **the process of Development, Evaluation, Applications & Extensions of the WCE methodology has <u>followed Most of the Phases identified by Heinze et al</u>** [*Biom J* 2024]

- Yet, Phase I included several distinct sub-phases and some of the elements of Phases II-IV were done in a different order
- In our experience, **Essential were the Inter-connections of Methodological Developments with Real-world Applications**:
  i. **Real-world analyses stimulated new methodological developments**, necessary to **address new analytical challenges (and identified some limitations of the method **)**
  ii. **WCE estimates provided new insights into, and generated new hypotheses about, the underlying biological processes linking time-varying exposures with the outcomes**

** E.g. in 1 drug application WCE has Not improved fit over conventional current use model: the reason was that Drug Doses remained very stable over time for most subjects

[Bally et al. *Pharmacoepidemiol Drug Saf 2018]* > ***<u>Phase III Conclusion:</u>*** ***WCE should be applied ONLY IF Individual Exposures show substantial Variation over Time!***

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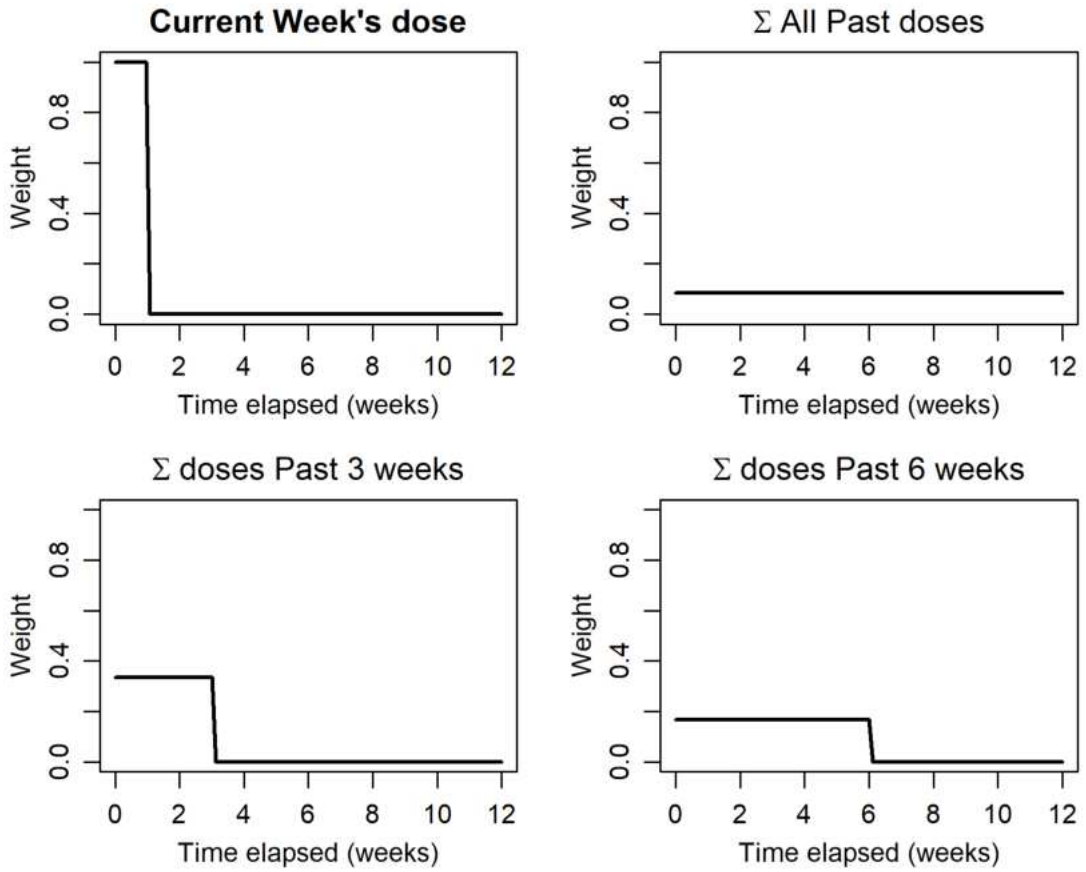
Phase "I C": (*cont-d*)
New Model: Concept & Formulation

- The proposed **WCE model includes several conventional exposure metrics as its special cases**, each with a different Weight function



Flexible WCE Model [Sylvestre & Abrahamowicz (2009)]

- **WCE in (2) is then modeled as a Time-Varying Covariate in Cox's model:**

(3)

where:

$h_0(u)$ is the baseline hazard

$\boldsymbol{X}(u) = \{X(t), 0 \leq t \leq u\}$ represents the time-vector of the past exposures

$Z_s(u)$, $s=1,\ldots,q,$ are the values of the fixed-in-time or time-dependent covariates relevant at time u

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

From equations (1), (2) & (3), the effect of WCE is modeled as:

$$WCE(u)=\sum_{t\le u} w(u-t) * X(t)=¿\beta\sum_{t}\sum_{j}\theta_j B_j(u-t) * X(t)¿$$

where BOTH β & θ_j need to be estimated.

To Avoid Identifiability Problems, we define:

$$\gamma_j=\beta\theta_j \qquad (4)$$

& construct Artificial Time-varying Covariates:

$$D_j(u)=\sum_{t}^{u} B_j(u-t)X(t) \qquad (5)$$

for *j=1,…,m*

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Given (4) & (5), the Cox's model in (3) becomes:

(6)

Once $D_j(u)$, $j=1,\ldots m$, are calculated for each u = uncensored event time, the model in (6) can be implemented using standard software for Cox's model with time-dependent covariates