Use of Data-Driven Simulations to inform Real-World Survival Analyses

Michal Abrahamowicz[*1]

Marie-Eve Beauchamp[2], Anne-Laure Boulesteix[3],
Tim P. Morris[4], Willi Sauerbrei[5], Jay S. Kaufman[1],
on behalf of the STRATOS Simulation Panel (SP)

[1] **McGill University, Montreal, Canada**
[2] Research Institute of the McGill University Health Centre, Montreal, Canada
[3] LMU Munich, Munich, Germany
[4] MRC Clinical Trials Unit at UCL, UCL, UK
[5] Medical Center - University of Freiburg, Freiburg, Germany

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Simulation Panel's Mission & Objective of the Current Study

- STRATOS Simulation Panel's Mission:

  Promote more widespread and more accurate use of simulations in both methodological and applied statistical research, through enhancing their:

  (i) Validity (lack of bias, neutrality) [Boulesteix et al., 2018]

  (ii) Reproducibility (accurate reporting, software availability) [Morris et al., 2019]

  (iii) Practical Relevance (plausibility)

- Current Study's Goal (focus on *Applied* research):

  To stimulate use of **data-driven simulations**

  to assess the **impact of specific imperfections in the available data**

  on the results of **real-world time-to-event analyses**

Boulesteix, Binder, Abrahamowicz et al,. *Biom J* 2018.
Morris, White, Crowther, *Stat Med* 2019.

Background: Need to be *more pro-active* when *dealing with imperfections of real-world data*

- Most real-world observational clinical/epi studies recognize (in Discussion) some imperfections in the available data and/or limitations of the study design that may affect the *accuracy* (or even *validity*?) of the results

- Traditionally, this was limited to a lip service, possibly with vague qualitative comments aimed at minimizing the problem**, *e.g.:*

  "Lack of data on disease severity might have affected some of our estimates, but similar problems are common to this area of research."

** Applies also to many papers co-authored by members of our team ☺

Our approach: Quantitative Bias Analysis (QBA) via Data-Driven Simulations

- To make results directly relevant for the data at hand, **we Combine:** Observed Multivariable Real-world data** with Simulating Additional Data items (outcomes and/or covariates) based on carefully defined assumptions

- To simulate time-to-event data **with time-varying exposure**(s)/covariate(s), we rely on the dedicated, validated, "Permutational Algorithm" [Sylvestre & Abrahamowicz, 2008]

** Note this Contrasts with traditional Methods-driven Simulations (in *statistical papers*) that often assess or compare performance of selected methods across a range of (usually hypothetical) plausible data structures

Sylvestre & Abrahamowicz, *Stat Med* 2008.

Implementation of Data-Driven Simulations: Preliminary Steps 1-3

3 Preliminary Steps:

(*see later slides for implementation in 2 illustrative examples)*

1) **Identify relevant Data Imperfection(s)** in your Available Real-World data & (if relevant) carry related Initial Data Analyses

2) Perform relevant, usually **Multivariable, Analyses of the Available Data to get 'naïve' estimates** (Not corrected for the Imperfection(s) identified in step 1) of the relationships between exposure, outcome, and covariates

3) Based on substantive knowledge and/or literature, **Formulate Assumption(s)** regarding how the *available data* can be modified or expanded to create the *oracle dataset* that is corrected for the expected impact of the imperfection identified in step 1 **

(** Several plausible alternative scenarios may be considered here, each implying repeating further steps 4-7)

Implementation of Data-Driven Simulations: Main Steps 4-7

Data Simulations & Analyses (Steps 4-6) to be independently repeated across *m* (e.g., 1000) replications*:

4) **Generate the 'Oracle data'** (**Free of the imperfections** of interest) that combine relevant empirical estimates from step 2 with additional data simulated according to the assumptions from step 3

5) **Modify the 'Oracle data'** from step 4 **to account for imperfection(s)** identified in step 1

6) **Analyze (6a) the 'Oracle' and (6b) the Modified (Imperfect) data** (from steps 4 *and* 5, respectively), *using the same methods*, and **contrast the corresponding results**

7) FINAL Step: **summarize the results** of step 6 across *m* replications and formulate the Conclusions regarding the Impact of the Data Imperfection

* Steps 4-7 must be repeated for each alternative simulated scenario identified in step 3

Example # 1: Impact of omitting cancer stage in a prognostic study of colon cancer mortality

- Goal of the analyses: estimate the independent (adjusted) association of **obstruction of the colon by a tumour ("exposure")** with **all-cause mortality ("outcome")** among patients diagnosed with colon cancer.

- Data source: publicly available dataset from the *survival* R package [Therneau, 2021], with N = 906 colon cancer patients, 175 (19.3%) with the colon obstructed, and 441 deaths during follow-up [Moertel et al., 1995]. Several time-invariant prognostic factors, measured at cancer diagnosis, are available, some associated with both (i) obstruction exposure and (ii) survival, calling for multivariable analyses.

Therneau, *Survival* R package 2021.
Moertel, Fleming, MacDonald et al., *Ann Int Med* 1995.

Example # 1: steps 1 - 3

- *Step 1 (**Imperfection**):* available data do *not* include cancer stage at diagnosis, a powerful predictor of mortality in colon cancer [Quantin et al, 1999], with higher stage likely associated with both obstruction exposure (i.e. potential unmeasured confounder) and some measured covariates

- *Step 2 (**Naïve analyses**):* multivariable Cox proportional hazards (PH) model, with adjustments for measured covariates (but NOT stage), yields **HR = 1.33 for colon obstruction (95% CI: 1.06; 1.68)**

- *Step 3 (**Substantive Assumptions**):* **higher cancer stage** at diagnosis (dichotomized: stage III-IV *versus* I-II) assumed to have **HR = 4.0 for mortality**, and **OR = 1.2 for colon obstruction**, as well as associations with selected measured covariates.
  4 alternative scenarios: with the true **HR = 1.0, 1.3, 1.5 or 2.0** for **colon obstruction.**

Quantin, Abrahamowicz, Moreau et al., *Am J Epidemiol* 1999.

Example # 1: Simulation Methods (*Step 4:* "Oracle data" generation)

- Step 4.1: Across scenarios & 1000 samples use (fixed) real-world data on:
  - (4.1.1) 906 multivariable X vectors (exposure + measured covariates)
  - (4.1.2) Outcomes: Times of 441 events (deaths) + 465 censorings

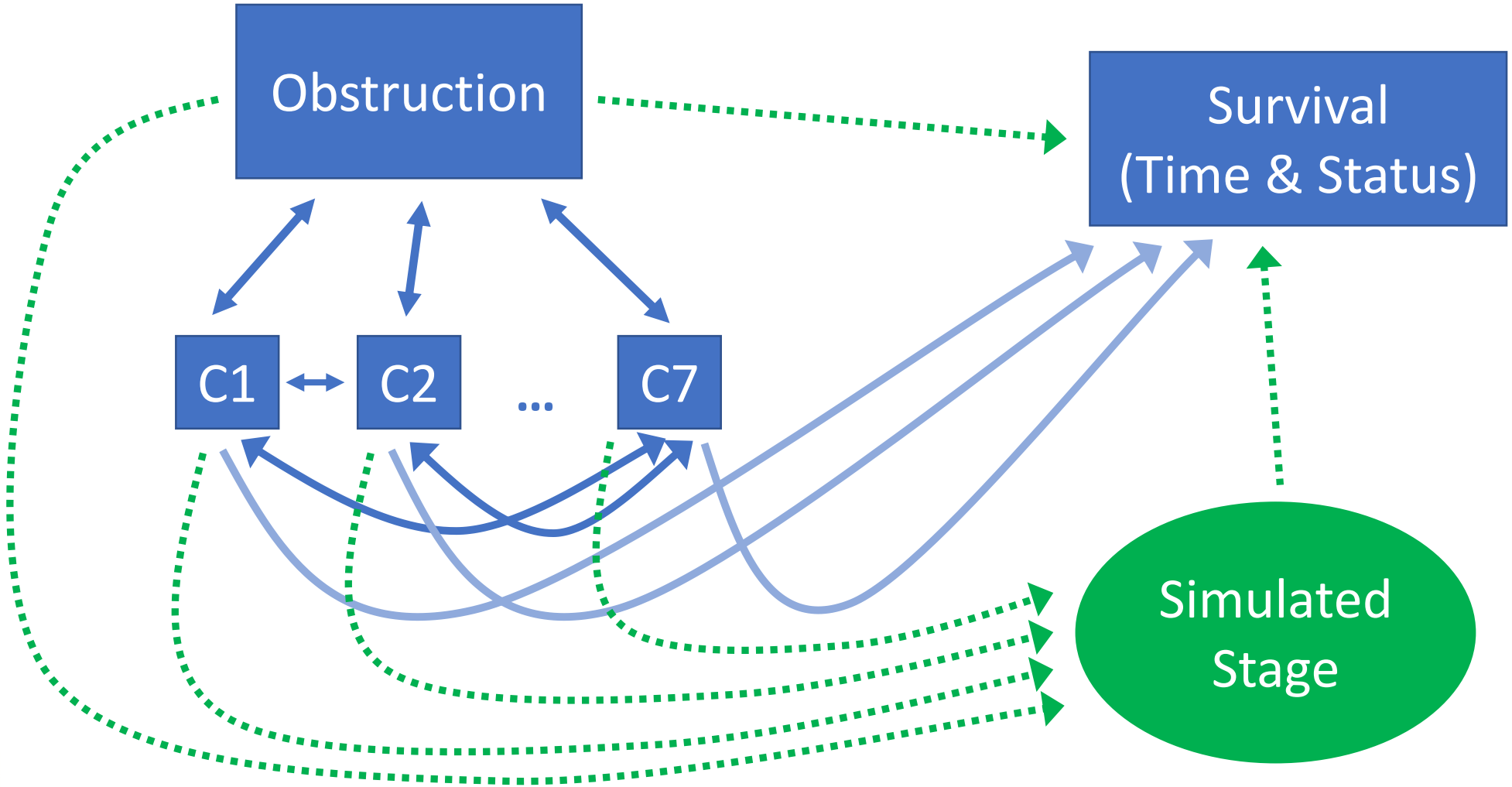
- Step 4.2: **{*Stage* | exposure, covariates} generated independently** in each sample, based on ORs assumed in step 3

- Step 4.3: Use **Permutational Algorithm to assign each of the events or censoring** obs. (with times from 4.1.2) **to one of the 906 'expanded' X vectors** (from 4.1.1 + Stage from 4.2) based on the 'true' PH model, with:

  (i) *Assumed HRs for Stage and Obstruction,* specified in step 3; and

  (ii) For *measured covariates: 'empirical' adjusted HRs estimates* from step 2

Example 1: Observed & Simulated
Data Structure



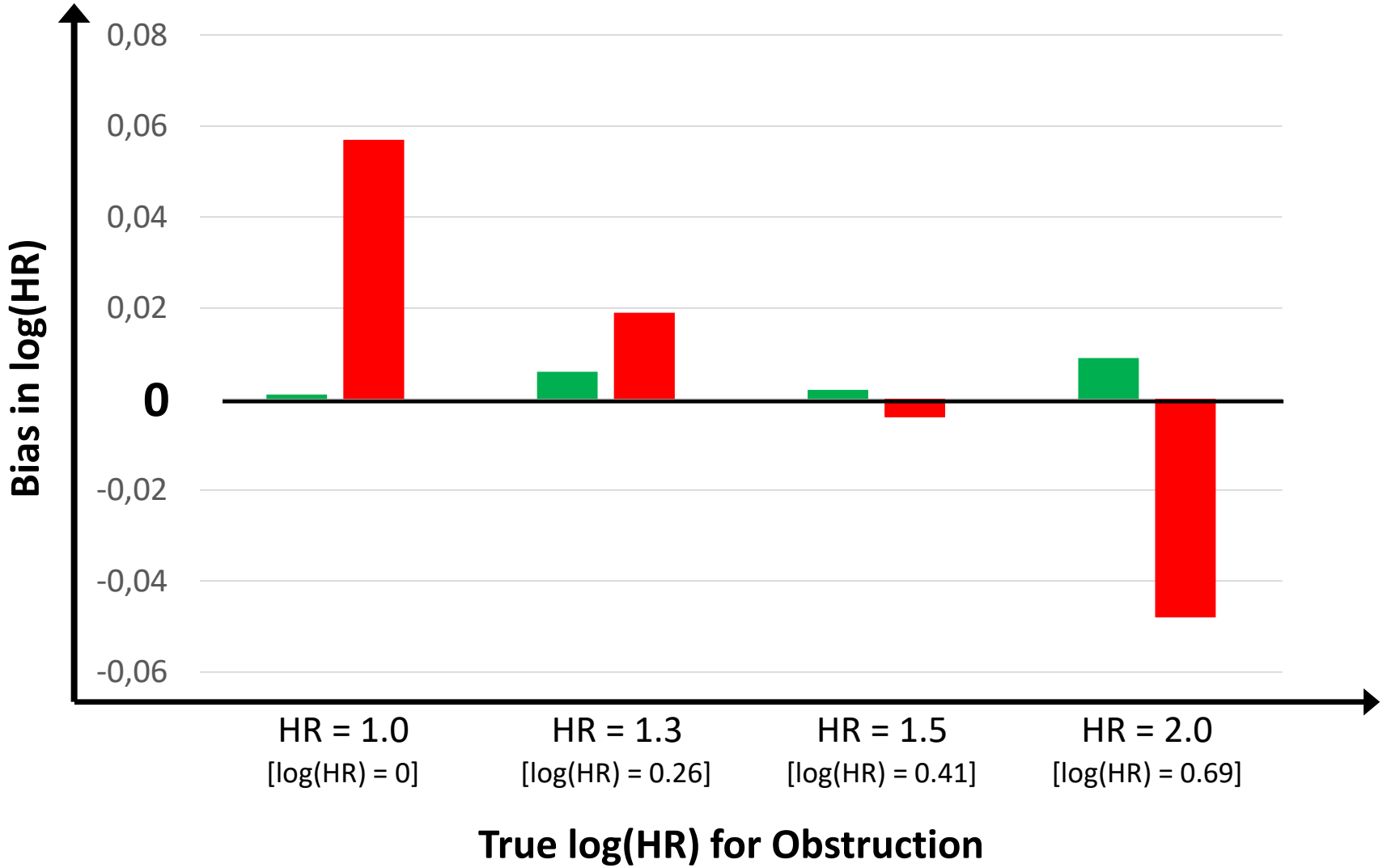
Example # 1: *Steps 5 - 7*

- *Step 5 (Modifying Oracle data to **Insert the Imperfection**):*
  each of *m* samples simulated in step 4 modified by **Deleting "Stage"**

- *Step 6 (**Analyses of (6a) Oracle vs (6b) Imperfect data**):*
  multivariable Cox PH models, with Colon Obstruction & all Measured Covariates, **Only Difference: Stage (6a) Included *vs*. (6b) Stage Excluded**

- *Step 7 (**Summarizing** the results):*
  focus on **BIAS *(Mean of 1000 Estimates – True)* in Adjusted log (HR)** *for Colon Obstruction:* **(6a) *vs*. (6b)**

Example # 1: BIAS in log(HR) for Obstruction as a function of 'true' HR: Oracle vs. Imperfect data



Example # 1: Conclusions

- **Lack of data on Cancer Stage has likely only a minor impact** on the accuracy of the adjusted log(HR) for Colon Obstruction
  (absolute Bias < 0.1, coverage rate of 95% CI: ≥ 90%)

- Expected Bias varies depending on the strength of the (assumed) true association**:
  - (i) Slight over-estimation of null or weak effects (1 ≤ HR ≤ 1.3) *versus*
  - (ii) Slight under-estimation of stronger effects (HR ≥ 1.5)

** Due to a **Combination** of (i) **Unmeasured Confounding** (OR = 1.2 for Stage-Obstruction) ***vs.*** (ii) **Non-Collapsibility** (HR = 4.0 for omitted Stage)

Example # 2: **Association of a Time-Varying exposure with an (imprecisely timed) Interval-Censored event**

- Goal of the analyses: estimate the association of **recent benzodiazepine use** with **cognitive impairment**

- Data source: ***synthetic data*** **based on real-world time-varying patterns of benzodiazepine use** [Bartlett et al., 2004], with N= 1250 new benzodiazepine users generating **285 (23%) events of cognitive impairment** during up to 3 years of follow-up. 2 measured time-invariant covariates: sex and age. **Binary Time-Varying Exposure (TVE) = Any Benzodiazepine use in the last 2 weeks**.

Bartlett, Abrahamowicz, Tamblyn, et al., *Pharmacoepidemiol Drug Saf* 2004.

Example # 2: Steps 1 - 3

- *Step 1 (**Imperfection**):* an event of **cognitive impairment is detected** only at the time of the first clinic visit after its actual occurrence, so the **actual event times remain unknown**, resulting in **Interval-Censored events (see Next Slide for Implications for TVE analyses)**

- *Step 2 (**Naïve analyses**):* 2 Cox PH models (adjusted for age & sex), with ***alternative Event Times Imputation:***

  (i) @ **END** of the Interval (visit when event 'detected'): HR(TVE) = **1.2**; (95%CI: **0.87**-1.68) *vs.*

  (ii) @ **MID-Point** of the Interval (between 2 adjacent visits): HR(TVE) = **1.47**; (95%CI: 1.09-2.00)

- *Step 3 (**Substantive Assumptions**):* **True (UN-known) event equally likely to occur at any time within the between-visit interval** at the end of which it was detected.

  4 alternative scenarios: with HR = 1.0, 1.5, 2.0 or 2.5 for TVE (recent benzodiazepine use)

Impact of inaccurate timing of interval-censored events on the associated 'current' values of time-varying exposure

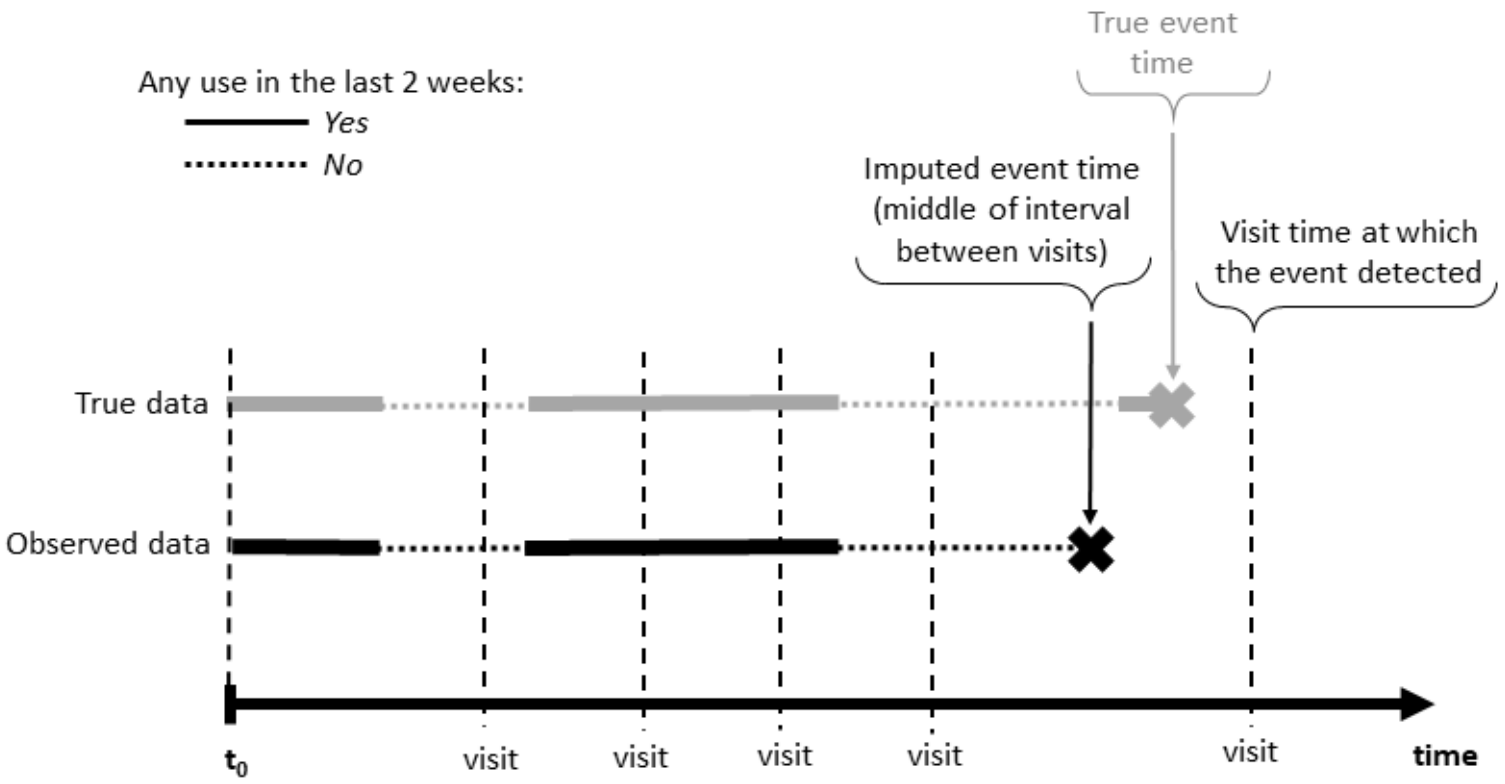


Illustration of the impact of inaccurate timing of interval-censored events for a hypothetical subject: the time-varying exposure metric "any use in the last 2 weeks" value differ between the true event time (exposure = yes) and the imputed event time (exposure = no) at the middle of the intervals between the visits when the event was detected and the preceding visit.

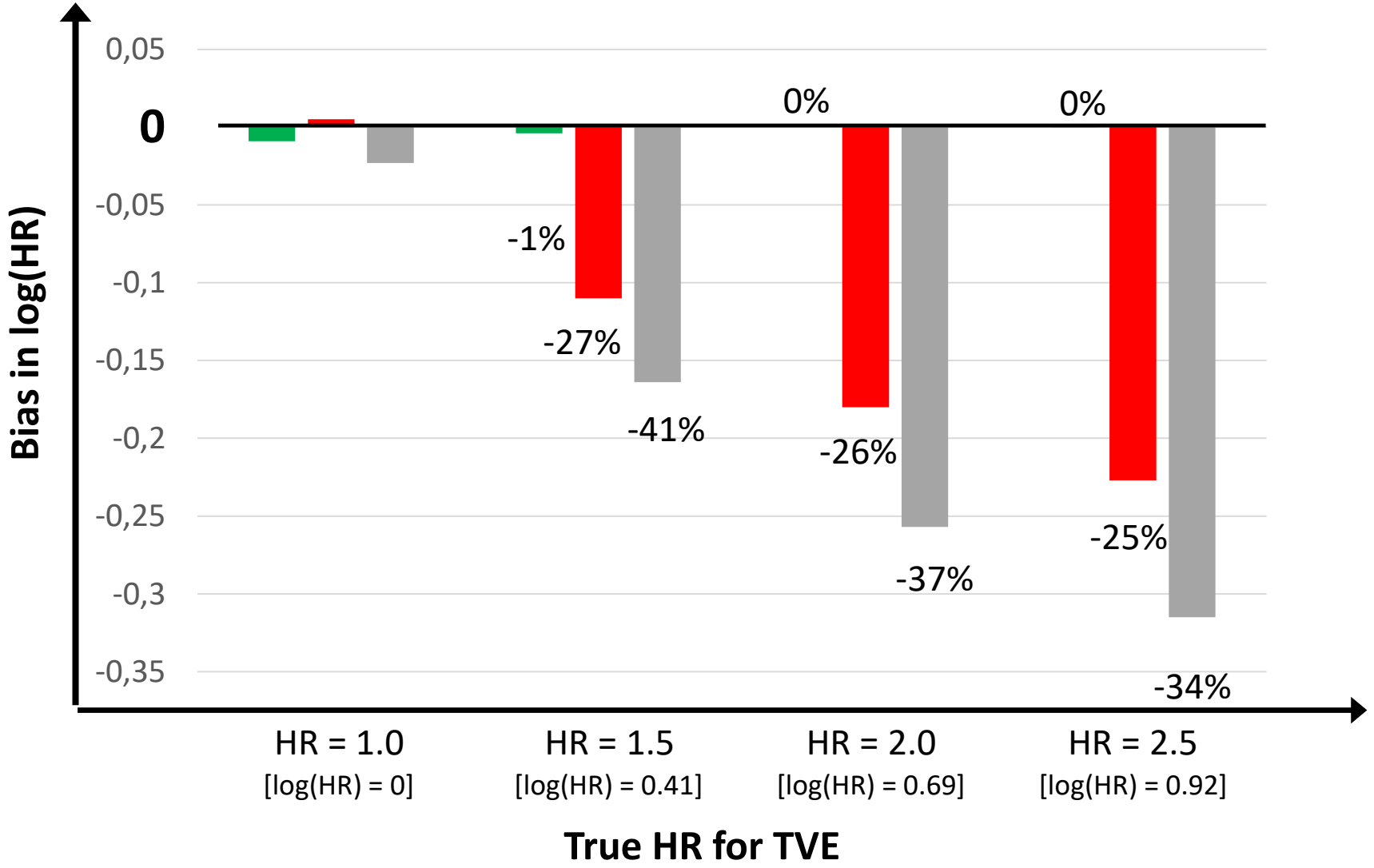
Example # 2: Steps 4 - 6

- *Step 4:* (**"Oracle data" generation):**
  - (4.1) Across scenarios & 1000 samples use (fixed) observed data on: 1250 TVE time-vectors (daily benzo use) with corresponding age & sex
  - (4.2) **"True" Time of event** i = 1,...,285 generated (independently for each of m samples) from ***Uniform U ~ [$t_{i,(j-1)}$; $t_{i,j}$] over the interval*** between the earlier visit $t_{i,(j-1)}$ and visit $t_{i,j}$ when it was detected
  - (4.3) Use **Permutational Algorithm to assign each of the events** obs. (with times from 4.2) **to one of the TVE vectors** (from 4.1) based on the 'true' PH model, with: (i) assumed HR for TVE (from step 3) and (ii) empirical HR estimates for age and sex (from step 2)

- *Step 5: (**Inserting the Imperfection**):* **Exact ('true') event times were Deleted** and only the times of the visits when events were detected were reported

- *Step 6: (**Analyses**): 3* **multivariable Cox models: (6a) Oracle data (True event times) *vs.* (6b) Event Times Imputed (Imperfect data) at: *(6b1) End (detection visit)* *or (6b2) Mid-point* *of the interval* [$t_{i,(j-1)}$; $t_{i,j}$]**

Example # 2: BIAS in log(HR) for TVE as a function of 'true' HR: Oracle vs. Imputation @: MID vs END



Example # 2:
Summary of Results & Conclusions

- **(i) Imprecise Timing of the events** (transient Cognitive Impairment) **induces considerable Bias to the Null in the estimated HR for the Time-Varying Exposure** (recent use of Benzodiazepines)

- **(ii) Bias is systematically stronger for Imputing the events at the End (~ 35-40% relative bias) than at the Mid-point (~ 25% relative bias) ** of the interval between the adjacent visits**

  (** Also, Root Mean Squared Error (RMSE) of End-imputed estimates is 20%-30% higher than for Mid-point-imputed estimates

- (iii) Given (i) & (ii), the **'naïve' estimate based on Mid-point Imputation** of event times [**HR = 1.47** (95%CI: 1.09-2.00)] **provides a solid evidence of Risk Increase associated with a recent Benzodiazepines use but likely Underestimates its strength !**

Conclusions

- **Carefully designed Data-Driven Simulations** can provide valuable insights regarding the **expected impact of a specific Data Imperfection** or Design Limitation on the results and conclusions of a **particular Real-World study**

- **<u>Our methods extend the QBA toolbox to address complexities of:</u>**
  - *Multivariable* data structures
  - *Time-to-Event* (Survival) analysis
  - *Time-Varying Exposures*/Covariates

  but further real-world applications are necessary to fully assess their practical usefulness/potential…

Thank you!

Michal.Abrahamowicz@McGill.ca

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Outline

- Background / Rationale
- Overview of the proposed Approach to Data-driven Simulations
- 2 Real-World Illustrations:
    1) *Imprecise timing of (**interval-censored) events*** associated with a ***time-varying exposure***
    2) *Omitting* an important risk factor (*potential Confounder*)
- Conclusions

Limitations of existing QBA approaches

- (A) Neither approach accounts fully for the complex Multivariable data structure actually encountered in a given real-world dataset (relationships of different covariates with (i) each other, (ii) exposure, and (iii) outcome)
- (B) Not well developed for Time-to-Event analysis (for which the outcome is often dichotomized, i.e. *Event Times are ignored*) [e.g., Barberio et al., 2021]
- (C) Not clear if/how to handle Time-Varying Exposures (or time-varying covariates) ?

Barberio, Ahern, MacLehose et al., *Clin Epidemiol* 2021.

Simulation results (Example 1): Impact of not adjusting for cancer stage on adjusted log(HR) estimates for colon obstruction

Scenario #	True HR obstruction	True OR obstruction ↔ stage	True HR stage	Performance measures for estimated obstruction log(HR)	Oracle model WITH stage	Original model withOUT stage
1	1.0	1.2	4.0	Bias	0.010	0.064
				SD of estimates	0.124	0.126
				RMSE	0.125	0.142
				Coverage rate 95% CI	0.947	0.900
				Type I error rate (%)	5.3	10.0
2	1.3	1.2	4.0	Bias (relative bias)	0.000 (0%)	0.016 (6.0%)
				SD of estimates	0.116	0.119
				RMSE	0.116	0.120
				Coverage rate 95%CI	0.953	0.951
				Power (%)	60.4	66.0
3	1.5	1.2	4.0	Bias (relative bias)	0.004 (0.9%)	-0.009 (-2.3%)
				SD of estimates	0.115	0.116
				RMSE	0.115	0.116
				Coverage rate 95%CI	0.963	0.950
				Power (%)	94.2	92.6
4	2.0	1.2	4.0	Bias (relative bias)	0.011 (1.5%)	-0.044 (-6.4%)
				SD of estimates	0.118	0.121
				RMSE	0.118	0.129
				Coverage rate 95%CI	0.940	0.921
				Power (%)	100	100

Background: Main existing approaches for Quantitative Bias Analysis (QBA)

- Recent studies incrementally rely on QBA to get a *Quantitative assessment of the potential impact of selected common data imperfections* (e.g., unmeasured confounder or exposure measurement error) [Lash et al., 2009]

- **2 main existing Alternative QBA approaches [Banack et al., 2021]:**

  1) *Analytical correction formulas* for selected, relatively simple analyses, including e.g. E-values for unmeasured confounding [Vanderweele & Ding, 2017], OR

  2) *Simulating Synthetic data*, with data structure generally similar to the real-world data used in a given empirical study

Lash, Fink, Fox, Springer 2009.
Banack, Hayes-Larson, Mayeda, *Epidemiol Rev* 2021.
Vanderweele, Ding, *Ann Int Med* 2017.

Simulation results (Example 1): continued

Scenario #	True HR obstruction	True OR obstruction ↔ stage	True HR stage	Performance measures for estimated obstruction log(HR)	Oracle model WITH stage	Original model withOUT stage
5	1.3	1.0	4.0	Bias	0.004 (1.5%)	-0.034 (-13.0%)
				SD of estimates	0.120	0.123
				RMSE	0.120	0.127
				Coverage rate 95% CI	0.953	0.948
				Type I error rate (%)	60.7	48.3
6	1.0	2.0	4.0	Bias (relative bias)	-0.006	0.214
				SD of estimates	0.120	0.116
				RMSE	0.121	0.243
				Coverage rate 95%CI	0.947	0.565
				Power (%)	5.3	43.5
7	1.3	2.0	4.0	Bias (relative bias)	0.002 (0.8%)	0.177 (67.7%)
				SD of estimates	0.119	0.120
				RMSE	0.119	0.214
				Coverage rate 95%CI	0.944	0.638
				Power (%)	60.4	95.9

Simulation results (Example 2): Comparison of estimates for time-varying recent benzodiazepine use

True HR exposure	Performance measures	Model 1: Oracle	Model 2: Events at MID intervals	Model 3: Events at END intervals
1.0	Bias	-0.011	-0.004	-0.025
	SD of estimates [ratio END/MID]	0.187	0.182	0.184 [1.01]
	RMSE [ratio END/MID]	0.188	0.182	0.185 [1.02]
	Coverage rate 95%CI	0.943	0.955	0.955
	% samples MID closer to TRUTH than END	48.6%		
1.5	Bias (relative bias, %) [ratio bias END/MID]	0.000 (-0.1%)	-0.105 (-26.0%)	-0.161 (-39.6%) [1.52]
	SD of estimates [ratio END/MID]	0.158	0.160	0.165 [1.03]
	RMSE [ratio END/MID]	0.158	0.192	0.230 [1.20]
	Coverage rate 95%CI	0.955	0.922	0.866
	% samples MID closer to TRUTH than END	59.5%		
2.0	Bias (relative bias, %) [ratio bias END/MID]	-0.009 (-1.3%)	-0.186 (-26.9%)	-0.252 (-36.4%) [1.35]
	SD of estimates [ratio END/MID]	0.150	0.151	0.154 [1.02]
	RMSE [ratio END/MID]	0.150	0.240	0.295 [1.23]
	Coverage rate 95%CI	0.948	0.779	0.672
	% samples MID closer to TRUTH than END	67.0%		
2.5	Bias (relative bias, %) [ratio bias END/MID]	-0.004 (-0.4%)	-0.230 (-25.1%)	-0.314 (-34.3%) [1.36]
	SD of estimates [ratio END/MID]	0.139	0.140	0.147 [1.05]
	RMSE [ratio END/MID]	0.139	0.269	0.347 [1.29]
	Coverage rate 95%CI	0.953	0.676	0.454
	% samples MID closer to TRUTH than END	72.5%		

Example # 1: Impact of omitting cancer stage in a prognostic study of colon cancer mortality

- Goal of the analyses: estimating independent (adjusted) association of **obstruction of the colon by a tumour ('exposure')** with **all-cause mortality ('outcome')** among patients diagnosed with colon cancer
- Data source: publicly available dataset from the *survival* R package [1, Therneau, 2021], with N=906 colon cancer patients, 175 (19.3%) with the colon obstructed, and 441 deaths during the follow-up [2, Moertel et al., 1995]. Several time-invariant prognostic factors, measured at cancer diagnosis, are available [1,2], some associated with both (i) obstruction exposure and (ii) survival, calling for multivariable analyses.
- *Step 1 (**Imperfection**):* the available data do *not* include cancer stage at diagnosis, a powerful predictor of mortality in colorectal cancer [Quantin, 1999], with higher stage likely associated with both obstruction exposure (i.e. potential unmeasured confounder) and some measured covariates
- *Step 2 (**Naïve analyses**):* multivariable Cox proportional hazards (PH) model, with adjustments for measured covariates (but NOT stage), yields **HR=1.33 for colon obstruction (95% CI:1.06; 1.68)**
- *Step 3 (**Substantive Assumptions**): 7 alternative scenarios:* **higher cancer stage** at diagnosis (dichotomized: stage III-IV *versus* I-II) assumed to have: **HR=4.0 for mortality**, and **OR=1.2 for colon obstruction** (*modified in some scenarios*), as well as associations with selected measured covariates. Across the scenarios, the true HR for the exposure **(colon obstruction) varied (HR= 1.0, 1.3, 1.5 or 2.0).**

Therneau, R package 2021.
Moertel, Fleming, MacDonald et al., *Ann Int Med* 1995.
Quantin, Abrahamowicz, Moreau et al., *Am J Epidemiol* 1999.