(*many*!) Analytical Challenges in Real-World studies of Drug Safety: If, Where & How Statistical Modeling may Help ?

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Objectives

- To use a Real-World pharmaco-epidemiological study of a specific drug to:
- 1) illustrate the Complex Analytical Challenges in Real-World research on Drug Effects;
- 2) outline how recent Progress in Statistical Modeling helps address some of these issues;
- 3) identify (selected) complex Methodological Challenges that require further Development of New Methods and/or Combining Existing approaches;

Example of a Challenging Observational Study: Hydrochlorothiazide use vs. Non-Melanoma Skin Cancer (NMSC)

Background:

- Hydrochlorothiazide (HCTZ) is a popular antihypertensive drug, known to increase the sensitivity of the skin to sunlight and UV radiation [2]
- UV exposure is an important risk factor for NMSC [3,4], the most common cancer worldwide
- Emerging evidence of NMSC risk associated with cumulative HCTZ exposure [5,6]

Objective:

To Respond to Health Canada (federal Ministry of Health) Query:
If and How NMSC risk increases with Cumulative Duration of HCTZ use?
(PI: Sasha Bernatsky, McGill)

[2] Blakely, *Drug Saf* 2019; [3] Kaae, *Cancer Epidemiol Biomark Prev* 2010; [4] Makhzoumi, *J Invest Dermatol* 2013;
[5] Pedersen, *J Am Acad Dermatol* 2018; [6] Drucker, *CMAJ* 2021

Study Overview

- *Data Source:* Population-based Observational study using Canadian Ontario Health Study (OHS) (>225,000 participants), 2006-2017
- *Exposure:* HCTZ use based on detailed history of filled Prescriptions (dates and duration)
- *Outcome:* Time of NMSC Diagnosis
- *Design:* "New user" design [7]: N = 2,844 incident elderly (>65 years) HCTZ users
- *Analysis:* Time-to-Event (Survival analysis)
- *Follow-up & Incidence:*
  - 13,523 person-years (mean=4.8 years, median=5.4, IQR: 3.3 – 6.2)
  - 222 (7.8%) NMSC diagnoses (events)
  - 16.4 NMSC cases per 1,000 person-years

[7] Ray, *NEJM* 2005

Design vs. Analysis ?

- Cohort vs. Nested Case-Control vs. Case-Cohort? [8]
- ***Proposed*** New users design (time 0 = 1st Rx for HCTZ) fits best with Cohort [7]
  - 2 latter designs *more efficient* but *not* well adapted to handle complex models for Time-Varying exposures

[7] Ray, *NEJM* 2005; [8] Gail, *BMJ* 2019; [9] Pazzagli, *PDS* 2018; [10] Cole, *AJE* 2005;
[11] Picciotto, *JASA* 2012; [12] Richardson, *Occup Environ Med* 2005; [13] Danieli, AJE 2019

Specific 'Design' challenge: Censoring criteria *vs* Drug Switching ?

- Many patients switch to another anti-hypertensive drug, which complicates the analysis [9]
- Right censor at Switch to another anti-hypertensive drug? **
- But Treatment switching is 'non-random' [10] -> Informative Censoring ?
- *Solutions:* Use IPCW and/or Structural Nested Accelerated Failure Time (SNAFT) model [11]?

** If Not censored at the switch: How to Separate effects of (i) "old" (HCTZ) vs. (ii) "new" drug?

- Censoring time needs to be delayed to account for **Lag (exposure → Cancer occurrence)** [12,13]

Choice of a Time-Varying Exposure metric

- **Exposure Metric needs to:**
  - Be **Time-Varying** to (i) avoid *immortal time bias* [14,15] and (ii) account for difference in timing and duration of past exposures
  - Account for **Lag (Latency)** for cancer occurrence [12]
  - Capture **Cumulative effects** of past exposures [9,15], which leads to **Further Challenges:**

❑ Unclear how long the effects of past HCTZ exposures may affect current NMSC hazard

➢ *Solution:* use goodness-of-fit to compare models with different "exposure windows" [16]

❑ The impact of past exposure likely depends on how long ago it occurred [12]

➢ *Solution:* use flexible models e.g. Weighted Cumulative Exposure [17], distributed lags [18] or penalized methods [19]

[9] Pazzagli, *PDS* 2018; [12] Richardson, *Occup Environ Med* 2005; [14] Suissa, *AJE* 2008; [15] Andersen, *Stat Med* 2021;
[16] Abrahamowicz, *Stat Med* 2012; [17] Sylvestre, *Stat Med* 2009; [18] Gasparrini, *Stat Med* 2014; [19] Bender, Biostat 2019

Exposure: Measurement error & misclassification

- (As in most pharmacoepidemiology database studies):

  Exposure history is re-constructed based on Filled Prescriptions [24,25]

- Yet, due to sub-optimal Treatment Adherence [26], such reconstructed Time-Varying Exposure does *not* correspond to the actual use of HCTZ [9], resulting in Berkson type of Measurement Error (ME) [27] for Exposure, which have less predictable impact on its estimated associations [28] than classical MEs [29]

- ME's in a Time-Varying Exposure/Covariate *X(t)* are difficult to handle [30]

- Possible *Solution:* recent simulations suggest that Simulation-Extrapolation (SIMEX) [31] methods can be adapted to correcting for MEs in a Time-Varying Exposures/Covariates [32]

[9] Pazzagli, *PDS* 2018; [24] Patorno, *Drug Saf* 2015; [25] Abrahamowicz, 2005; [26] Funk, *Curr Epi Rep* 2014; [27] Berkson, *Biometrics* 1950
[28] Potgieter, *Biometrics* 2016; [29] Shaw, Stat Med 2020; [30] Andersen, *Biostat* 2003; [31] Cook, *JASA* 1994; [32] Wang, *Biom J* 2020

Outcome & Modeling: Survival Analysis

- Which regression model? (re: exposure/covariates effects) [15]:

  Cox's proportional hazards (PH) [33] *vs.* **Accelerated Failure Time** (AFT) [34,35] *vs.* **Additive Hazards** (AH) [36,37]?

- Use **Marginal Structural Models** (MSM) to **account for Time-Varying confounders/mediators** [38,39]?

- Need to test model assumptions and account for violations [15] of PH [40,41,42], AH, or AFT [43]

[15] Andersen, *Stat Med* 2020; [33] Cox, *JRSSB* 1972; [34] Cox, 1984; [35] Komárek, *J Comput Grap Stat* 2005; [36] Aalen, *Stat Med* 1989; [37] Martinussen, *Biometrics* 2008; [38] Hernan, Epidemiol 2000; [39] Xiao, JASA 2014; [40] Therneau, 2000; [41] Abrahamowicz, *JASA* 1996; [42] Royston, *Stat Med* 2002; [43] Crowther, 2020; [44] Sabathé, *SMMR* 2020; [45] Oh, *Stat Med* 2018; [46] Clark, *Inj Epidemiol* 2014

Interval Censored Outcomes

- Inaccurate Timing of the Event (Interval-Censored outcome)**:

  NMSC can be diagnosed only at clinic visits to a physician with one of the relevant specialties [15]

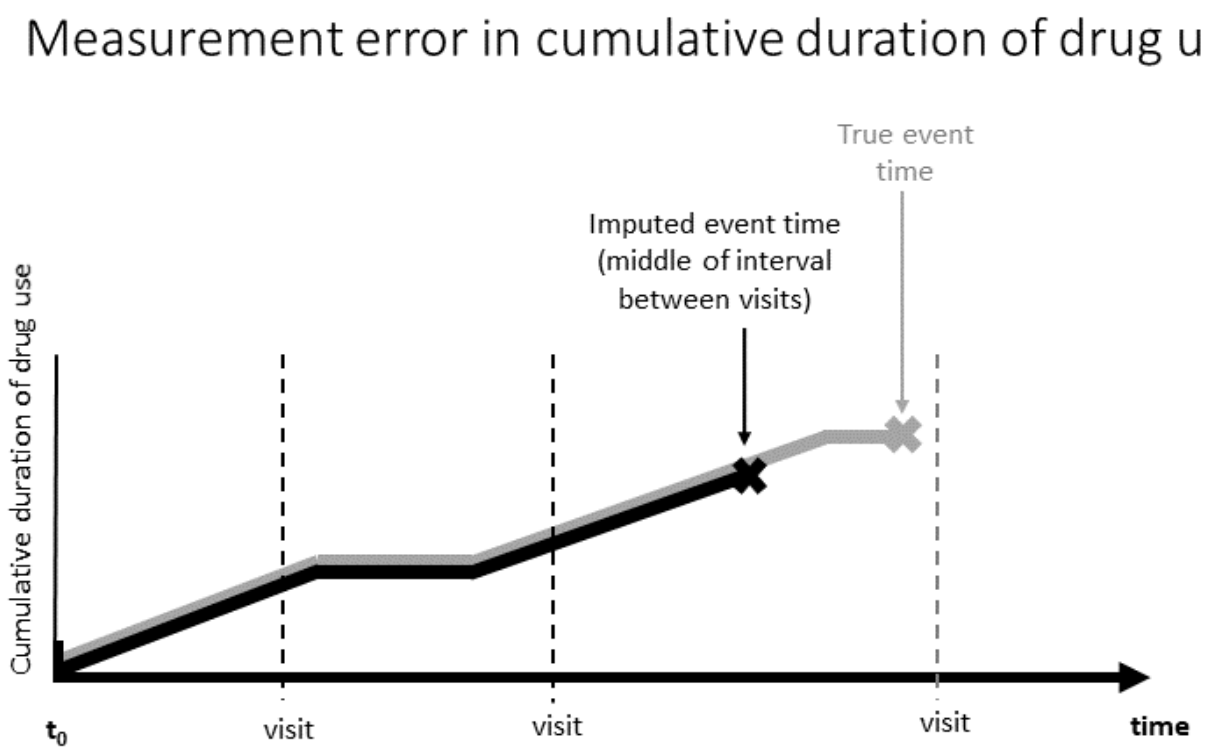
  (**Across the 222 NMSC cases, the mean difference between the 1st visit with NMSC diagnosis and the previous visit when it could be potentially diagnosed was 7.6 months

  (Me=5.1, IQR: 2.9 – 9.2))

- Interval-Censored Events (ICE) require specialized methods to avoid biased (usually toward the null) estimates [44,45]. Yet, existing ICE software does *not* accommodate Time-Varying exposures/covariates [46].

[15] Andersen, *Stat Med* 2020; [33] Cox, *JRSSB* 1972; [34] Cox, 1984; [35] Komárek, *J Comput Grap Stat* 2005; [36] Aalen, *Stat Med* 1989; [37] Martinussen, *Biometrics* 2008; [38] Hernan, Epidemiol 2000; [39] Xiao, JASA 2014; [40] Therneau, 2000; [41] Abrahamowicz, *JASA* 1996; [42] Royston, *Stat Med* 2002; [43] Crowther, 2020; [44] Sabathé, *SMMR* 2020; [45] Oh, *Stat Med* 2018; [46] Clark, *Inj Epidemiol* 2014

Errors in Cumulative Exposure due to Interval Censoring of the event times

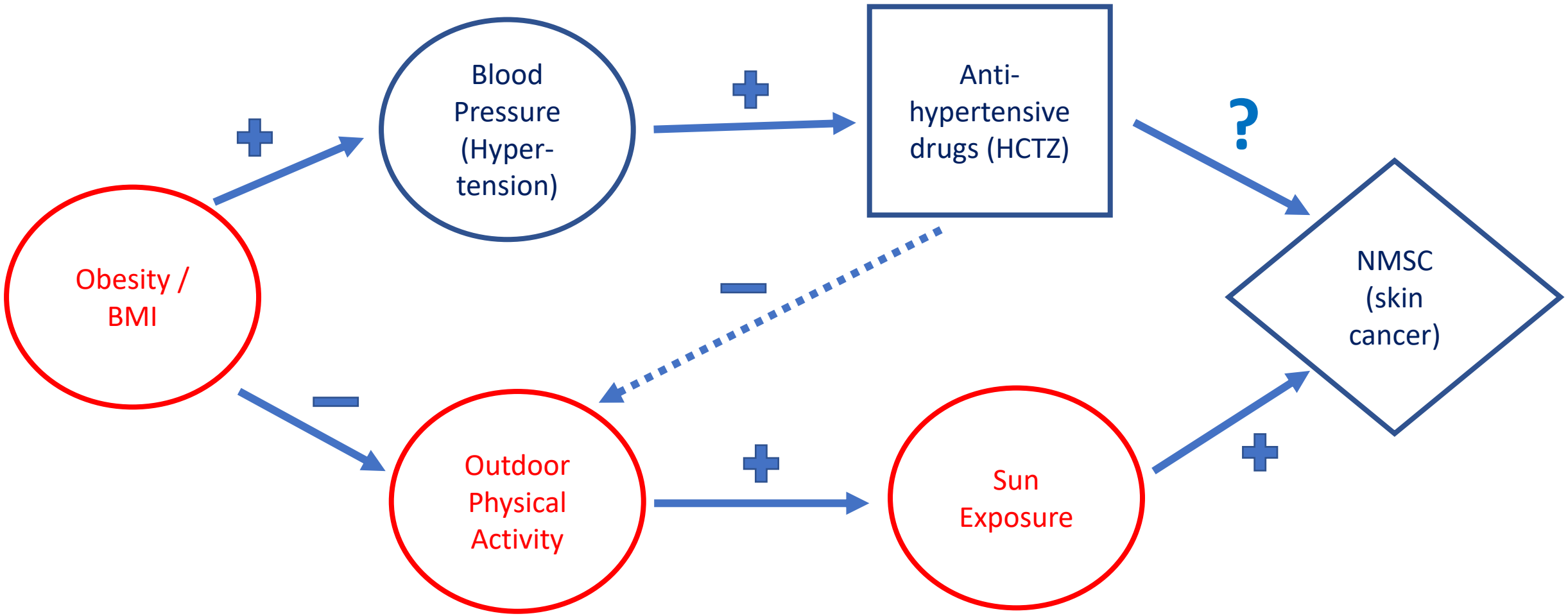


Residual Confounding vs Modeling of measured Covariates in Survival Analyses

- To avoid residual confounding [48], need to account for Non-linear (NL) effects of continuous confounders [49]
- *Further Questions/Challenges:* (i) How to model NL effects, e.g.: fractional polynomials [50] *or* splines [51]? Which of the many spline packages/approaches [52]?
- (ii) based on statistical criteria, a covariate may be erroneously excluded if its NL effect is not accounted for [53];
- (iii) in survival analysis, NL and Time-Dependent (TD, e.g. non-PH) effects of continuous covariates must be simultaneously assessed to avoid biased estimates and/or incorrect conclusions [54,55]
- *Potential Solution:* flexible modeling of NL & TD effects of Time-Varying covariates (e.g. our Cumulative Duration of HCTZ use) was recently validated [32]

[32] Wang, *Biom J* 2020; [47] Sauerbrei, *Diagn Progn Res* 2020; [48] Brenner, *Epidemiol* 1997; [49] Benedetti, *Stat Med* 2004;
[50] Royston, 2008; [51] Binder, *Stat Med* 2013; [52] Perperoglou, *Stat Med* 2019; [53] Wynant, *Stat Med* 2014;
[54] Abrahamowicz, *Stat Med* 2007; [55] Sauerbrei, *Biom J* 2007

DAG to identify potential Confounders and/or Mediators for HCTZ → NMSC association



Imputing (partly) Un-measured Confounders in Survival Analyses

- *Opportunity:* Unmeasured Confounders BMI and Physical Activity (PA) are available for only a small Subsample of participants through Clinical data (BMI) and Patients Self-reports (PA) Linked to the main OHS database
- *Analytical Challenge:* Choose a method to impute (possibly Time-Varying) Confounders measured only in a Validation Subsample (VS) in Survival Analyses
- Methods for Imputation of Missing Data depend on the setting [56]
- Most pharmacoepidemiology studies with access to VS use Propensity Score Calibration (PSC) [57].
- Yet, imputation is more accurate if it accounts for individual Outcomes [58], which is more challenging for Censored Survival data, where the outcome is 2-dimensional (time & status) [59].
- *Possible Solutions:* (i) White & Royston's approach [59] or (ii) Burne & Abrahamowicz's Martingale Residuals(MR) method [60], extended to imputation of Time-Varying Confounders used for IPTW in MSM analyses [61]

[56] Lee, *JCE* 2021; [57] Sturmer, *AJE* 2005; Moons, *JCE* 2006; [58] Moons, *JCE* 2006; [59] White, *Stat Med* 2009;
[60] Burne, *Stat Med* 2016; [61] Burne, *SMMR* 2019

Further Analytical Challenges:

- Outdoor Activities may act as a Mediator for HCTZ exposure (**DAG**). Yet, Mediation in Survival analyses requires complex methods [62,63].
- Important to assess Absolute Risks [15,64,65] (in addition to Relative Risks), while accounting for Censoring, which requires a careful choice of causal estimand(s) [66]. *Solution:* Recent methods allow estimating individual Survival Curves conditional on Time-Varying Covariates/Effects in flexible extensions of PH [42,67] and AFT [43] models. This will allow estimating differences in e.g. Restricted Mean Survival [68] associated with specific HCTZ use patterns.

[15] Andersen, *Stat Med* 2020; [42] Royston, *Stat Med* 2002; [43] Crowther, 2020; [62] Fulcher, *Epidemiol* 2017; [63] VanderWeele, *Epidemiol* 2011; [64] Gail, JNCI 1989; [65] Pfeiffer, 2018; [66] Goetghebeur, *Stat Med* 2020; [67] Wynant, *Stat Med* 2016; [68] Conner, *Stat Med* 2019; [69] Wynants, *BMC Med* 2019; [70] Van Calster, *BMC Med* 2019; [71] Heagerty, *Biometrics* 2000; [72] Saha-Chaudhuri, *Biostat* 2013; [73] Shen, *Biometrics* 2015

Conclusions

- Observational studies of Real-World effects of Drug Use pose several analytical challenges
- Recent progress in statistical modeling methods helps address many (but NOT All!) issues
- Some frequently encountered challenges require **combining expertise from different areas of statistical research**
- Often, there are **several alternative statistical approaches** but little solid evidence re:
  i. **Which method(s) work best?**
  ii. How their **relative performance depends on data structure?**

  So **further simulation studies** may be useful
- Other **complex issues require new analytical developments**

Thank you / Merci

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