Multiple analytical challenges in observational studies of health: goals and approaches of the STRATOS initiative

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on behalf of the STRATOS Initiative

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STRATOS INITIATIVE

McGill

PROBLEMS with Practical Applications of Statistical methods

The Economist **(October 2013):**
Unreliable research: Trouble at the lab.

"***Scientists' grasp of statistics has not kept pace with the development of complex mathematical techniques for crunching data.***

Some scientists use inappropriate techniques because those are the ones they feel comfortable with; others latch on to new ones without understanding their subtleties.

Some just rely on the methods built into their software, even if they don't understand them."

NEED for GUIDANCE

- Profusion of new, complex statistical techniques and algorithms
- Unclear which methods are useful in practice, and under what conditions?
- Insufficient awareness and understanding, among practitioners, of both well-established and, especially, new approaches and methods
- For some complex analytical challenges, there is *no* consensus, even among experts, as to the best approach
- Very **limited guidance** on key issues that are **vital in practice** discourages analysts from utilizing possibly more appropriate methods in their real-life applications, thus, reducing the scientific yield of empirical research

STRATOS Initiative: STRengthening Analytical Thinking for Observational Studies

- **The overarching long-term goal:**

  To improve design and statistical analyses of observational studies in practice

  by '*closing the gap*' between (i) recent relevant developments in statistical methodology *versus* (ii) methods applied in real-life observational studies

- Specific aims:
  - Develop **evidence-supported guidance** for statistical issues of practical importance (*through discussions among experts with different views, and simulations to systematically assess and compare alternative methods*)
  - Provide **guidance at several levels** of statistical knowledge
  - Start with **state-of-the-art** guidance for issues where there is consensus and necessary evidence
  - **Identify and explore complex analytical challenges requiring more primary research** and/or **combining expertise** in different areas of statistical research

STRATOS Milestones
http://www.stratos-initiative.org/

- **2013: Initiative launched** at 44th Int Soc Clin Biostatistics (ISCB) conference
- **2014: 1st STRATOS paper [1]:** *Statistics in Medicine* 2014; 33(30):5413-5432.

  Sauerbrei W, Abrahamowicz M, Altman D, le Saskia, Carpenter J. *STRengthening Analytical Thinking for Observational Studies: The STRATOS initiative.*
- **2016 & 2019: 2 General meetings**, Banff Int Res Station (BIRS), Canada
- **By 2021: >100 members (from 19 countries on 5 continents)**
- **Invited STRATOS Sessions and Mini-Symposia:**
  - Int Soc Clin Biost (ISCB): 2014, 2015, 2016, 2018, 2019, 2020, 2021
  - Int Biometric Conf (IBC): 2016, 2020 + Regional IBS meetings: 2017, 2018, 2021
  - Royal Statistical Soc (RSS): 2018, 2021
  - Soc Epi Res (SER): 2021
  - Other international conferences: HEC 2016, CEN 2018, GMDS 2017

STRATOS Topic Groups (TGs)

Topic Group		Chairs
1	**Missing data**	James Carpenter (UK), Kate Lee (AUS)
2	**Selection of variables and functional forms in multivariable analysis**	Georg Heinze (AUT), Aris Perperoglou (UK), Willi Sauerbrei (GER)
3	**Initial data analysis**	Marianne Huebner (US), Saskia le Cessie(NL), Carsten Oliver Schmidt (GER)
4	**Measurement error and misclassification**	Laurence Freedman (ISR), Victor Kipnis (US)
5	**Study design**	Mitchell Gail (US), Suzanne Cadarette (CAN)
6	**Evaluating diagnostic tests and prediction models**	Ewout Steyerberg (NL), Ben van Calster (NL)
7	**Causal inference**	Els Goetghebeur (BEL), Ingeborg Waernbaum (SWE)
8	**Survival analysis**	Michal Abrahamowicz (CAN), Per Kragh Andersen (DEN), Terry Therneau (US)
9	**High-dimensional data**	Lisa McShane (US), Joerg Rahnenfuehrer (GER), Riccardo de Bin (NOR)

STRATOS Cross-cutting Panels

Panel		Chairs and Co-Chairs	
MP	**Membership**	Chairs:	James Carpenter (UK), Willi Sauerbrei (GER)
PP	**Publications**	Chairs:	Bianca De Stavola (UK), Pam Shaw (US)
		Co-Chairs:	Mitchell Gail (US), Petra Macaskill (AUS)
GP	**Glossary**	Chairs:	Martin Boeker (GER), Marianne Huebner (US)
WP	**Website**	Chairs:	Joerg Rahnenfuehrer (GER), Willi Sauerbrei (GER)
RP	**Literature Review**	Chairs:	Gary Collins (UK), Carl Moons (NL)
BP	**Bibliography**	Chairs:	to be determined
SP	**Simulation Studies**	Chairs:	Michal Abrahamowicz (CAN), Anne-Laure Boulesteix (GER)
DP	**Data Sets**	Chairs:	Saskia Le Cessie (NL), Maarten van Smeden (NL)
TP	**Knowledge Translation**	Chair:	Rolf Groenwold (NL), Maarten van Smeden (NL)
CP	**Contact Organisations**	Chairs:	Willi Sauerbrei (GER)
VP	**Visualisation**	Chairs:	Mark Baillie (SWITZ/CH)

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?

[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:* 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

Challenges at Intersection of: Design (TG5), Survival Analysis (TG8) and Causal Inference (TG7)

- New users design (time 0 = 1st Rx for HCTZ) [7]
- Cohort vs. Nested Case-Control vs. Case-Cohort? [8]
  - 2 latter designs *more efficient* but *not* addressed by some complex models for TV exposures
- 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]

[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

Time-Varying Exposure metric: Intersection of Design (TG5) & Causal Inference (TG7) & Survival (TG8)

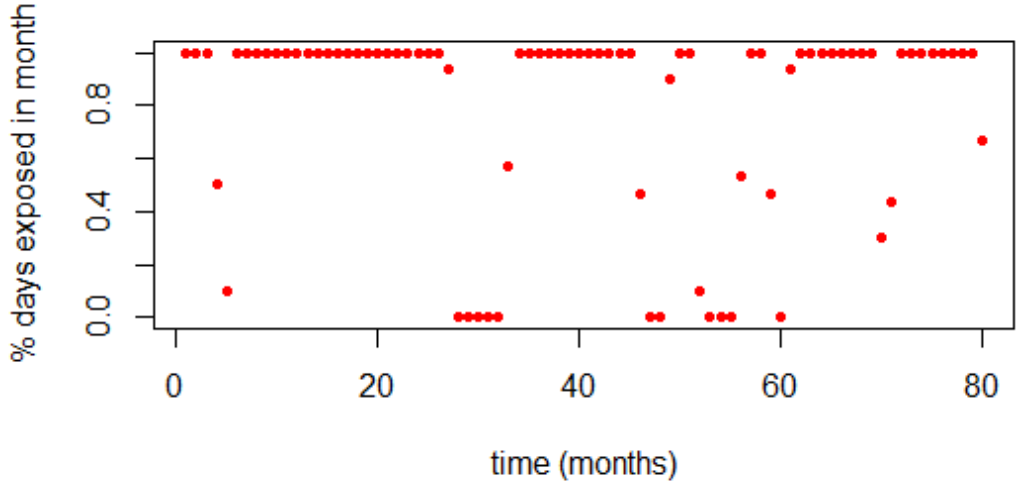
- **Exposure Metric needs to:**
  - Be Time-Varying to avoid *immortal time bias* [14,15]
  - Account for Lag (Latency) for cancer occurrence [12]
  - Capture Cumulative effects of past exposures [9,15]

- **Further Challenges and possible solutions:**
  - 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

Initial Data Analysis (TG3) & Visualisation panel

- How to summarize distributions of Time-Varying Exposure ?
  (TVE, here: Cumulative Duration of HCTZ use)



- Conventional Descriptive statistics may be misleading for TVE's [20]:
  - E.g., **Median Total Duration of HCTZ exposure** (over entire follow-up):
    NMSC cases = 1.7 year vs. "**Controls" (free of NMSC) = 2.9 years**
  - Suggesting *protective effect* of longer exposures, due to sort of "Immortal Time Bias" ("Length bias" due to **shorter follow-up for cases (Me = 3.3 years)** than **controls (Me = 5.7 years)**
  - possible *Solution:* use **Profile Plots** [21,22,23]

[20] Huebner, *BMC Med Res Methodol* 2020; [21] Cook, 2007; [22] Weiss, 2005; [23] Wang, *Stat Biopharm Res* 2020

Exposure: Measurement error & misclassification (TG4)

- 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 and may be related to (i) inaccurate measurement of *X(t)* values observed continuously during follow-up, and/or (ii) sparse observations of *X(t)* only at discrete times (e.g. clinic visits) [30]

- Possible *Solution:* recent simulations suggest that SIMEX [31] can be adapted to correcting for MEs in a TVC, in the context of flexible modeling of possibly Non-linear (TG2) effects of a continuous TVC in survival analysis [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 (TG8)

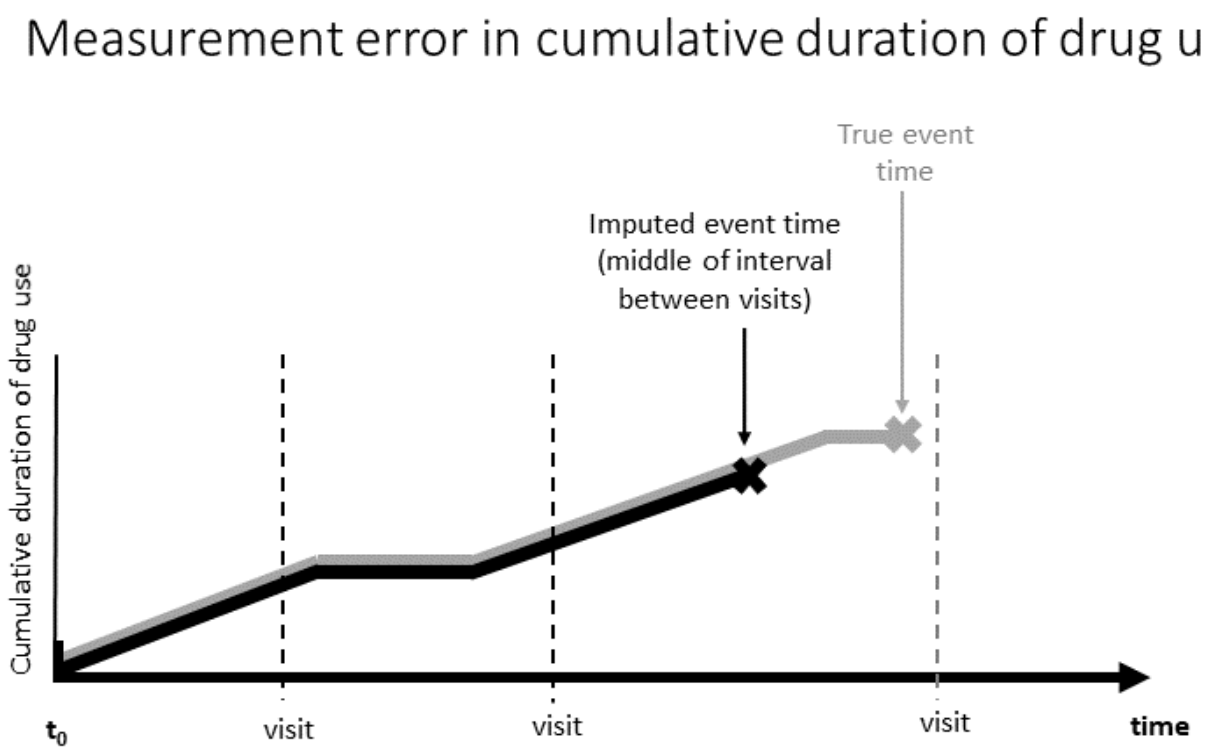
- Which regression model? (re: exposure/covariates effects) [15]:
  Cox's proportional hazards (PH) [33] *vs.* Accelerated Failure Time (AFT) [34,35] *vs.* Additive Hazards (AH) [36,37]?
- Use Marginal Structural Models (MSM) to account for Time-Varying confounders/mediators [38,39]?
- Need to test model assumptions and account for violations [15] of PH [40,41,42], AH, or AFT [43]
- 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

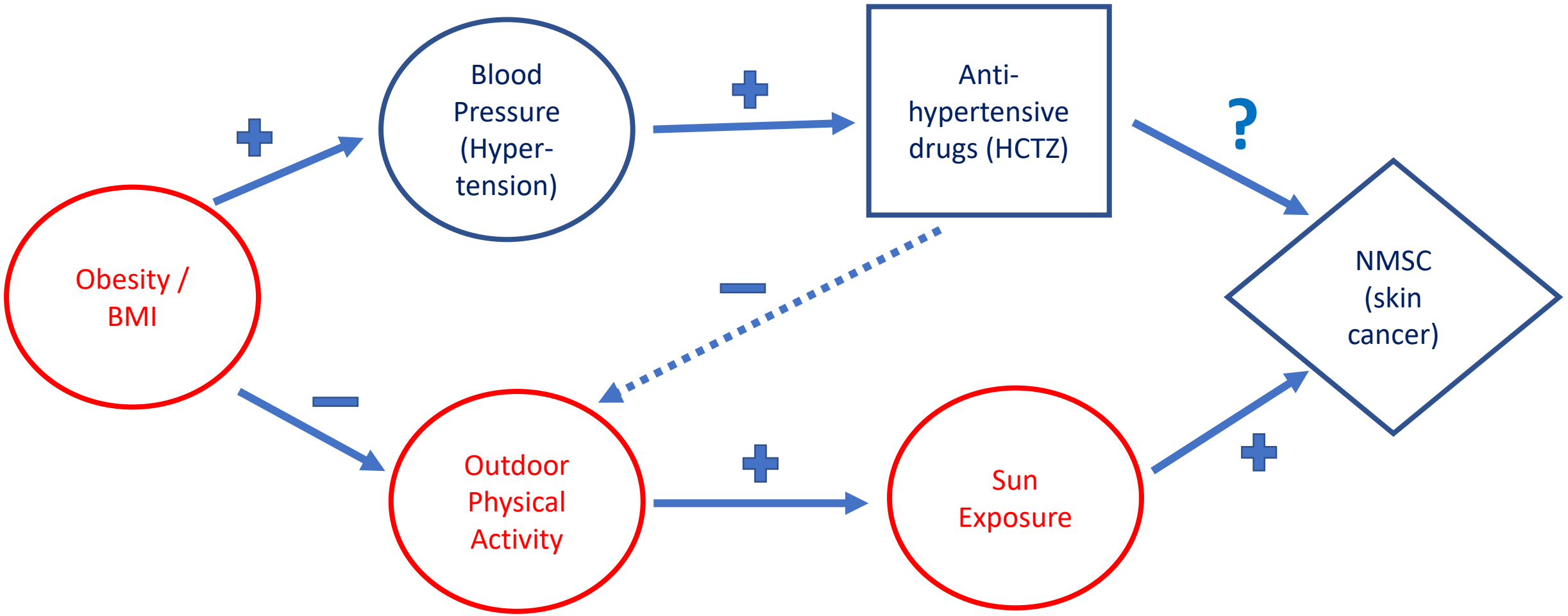


Covariates (selection & modeling):
Selection of variables and functional forms (TG2)

- **No consensus** in statistical literature re: state-of-the-art approach(es) to select covariates in multivariable regression models [47]
- 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

Causal Inference (TG7): DAG to identify Unmeasured Confounders for HCTZ → NMSC association



Imputing Unmeasured Confounders: Intersection of Missing Data (TG1) & Causal Inference (TG7) & Survival (TG8)

- *Opportunity:* Unmeasured Confounders BMI and Physical Activity (PA) are available for a 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 approach [59] or (ii) 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: Evaluating Prediction Models (TG6), Causal Inference (TG7) & Survival (TG8)

- 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.

- Finally, it is important to assess and compare Predictive Performance of alternative models [69,70]. *Solution: r*ecent methods allow estimating Time-Dependent ROC curves to assess the predictive accuracy of Time-to-Event models with Time-Varying covariates/exposures [71,72,73].

[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 pose several analytical challenges
- Some frequently encountered challenges require **combining expertise from different areas of statistical research**
- For some issues, 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**
- Many of these *state-of-the-art* issues are addressed in recent Tutorial papers by STRATOS Topic Groups **(examples on 2 next slides)**
- Future STRATOS **guidance for data analysts with limited statistical background** will focus on (i) **choice of appropriate easy-to-implement methods** and (ii) **limitations of some popular approaches**

TG1: Missing data

[56] Lee KJ, Tilling K, Cornish RP, Little RJ, Bell ML, Goetghebeur E, Hogan JW, Carpenter JR. Framework for the Treatment And Reporting of Missing data in Obeservational Studies: The TARMOS framework. ***J Clin Epidemiol*** 2021; 134:79-88.

TG2: Selection of variables and functional forms in multivariable analysis

[47] Sauerbrei W, Perperoglou A, Schmid M, Abrahamowicz M, Becher H, Binder H, Dunkler D, Harrell Jr. FE, Royston P, Heinze G. State of the art in selection of variables and functional forms in multivariable analysis - outstanding issues. ***Diagn Progn Res*** 2020; 4:3.

[52] Perperoglou A, Sauerbrei W, Abrahamowicz M, Schmid M. A review of spline function procedures in R. ***BMC Med Res Methodol*** 2019; 19(1):46.

TG3: Initial data analysis

[20] Huebner M, Vach W, le Cessie S, Schmidt CO, Lusa L. Hidden analyses: a review of reporting practice and recommendations for more transparent reporting of initial data analyses. ***BMC Med Res Methodol*** 2020; 20(1):61.

TG4: Measurement error and misclassification

[74] Keogh RH, Shaw PA, Gustafson P, Carroll RJ, Deffner V, Dodd KW, Küchenhoff H, Tooze JA, Wallace M, Kipnis V, Freedman L. STRATOS guidance document on measurement error and misclassification of variables in observational epidemiology: Part 1 - Basic theory and simple methods of adjustment. ***Stat Med*** 2020; 39(16):2197-2231.

[29] Shaw PA, Gustafson P, Carroll RJ, Deffner V, Dodd KW, Keogh RH, Kipnis V, Tooze JA, Wallace MP, Küchenhoff H, Freedman LS. STRATOS guidance document on measurement error and misclassification of variables in observational epidemiology: Part 2 - More complex methods of adjustment and advanced topics. ***Stat Med*** 2020; 39(16):2232-2263.

TG5: Study design

[8] Gail MH, Altman DG, Cadarette SM, Collins G, Evans SJ, Sekula P, Williamson E, Woodward M (2019): Design choices for observational studies of the effect of exposure on disease incidence. ***BMJ open*** 2019; 9:e031031.

TG6: Evaluating diagnostic tests and prediction models

[69] Wynants L, van Smeden M, McLernon DJ, Timmerman D, Steyerberg EW, Van Calster B. Three myths about risk thresholds for prediction models. ***BMC Med*** 2019; 17:192.

[70] Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. ***BMC Med*** 2019; 17:230.

TG7: Causal inference

[66] Goetghebeur E, le Cessie S, De Stavola B, Moodie EE, Waernbaum I. Formulating casual questions and principled statistical answers. ***Stat Med*** 2020; 39:4922–4948.

TG8: Survival analysis

[15] Andersen PK, Perme MP, van Houwelingen HC, Cook RJ, Joly P, Martinussen T, Taylor JMG, Abrahamowicz M, Therneau TM. Analysis of time-to-event for observational studies: Guidance to the use of intensity models. ***Stat Med*** 2020; 40:185–211.

Simulation panel

[75] Boulesteix AL, Binder H, Abrahamowicz M, Sauerbrei W. On the necessity and design of studies comparing statistical methods. ***Biom J*** 2018; 60(1):216-218.

THANK YOU!

Learn more about STRATOS structure, approach and Publications on

http://www.stratos-initiative.org/

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12. Richardson DB, Ashmore JP. Investigating time patterns of variation in radiation cancer associations. ***Occupational and Environmental Medicine*** 2005; 62(8):551–558.

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