UNSW CRAIC: Prevalent new-user cohort design

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https://github.com/mbg-unsw/pnuc

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Talk outline

- What & why
- Literature review
- In context
- Step by step
- Example
- Developments

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Why *prevalent* new-user?

- *i.e.* Compare those staying on old tx with switchers to new
- Increase sample size if few treatment-naive patients
- Better external validity if disease progression
- Key feature: conditioning on length of exposure
- Alternative to Marginal Structure Models (MSM)

Popularity of the PNUC design

- Lit review of PNUC to 9 May 2022
- 19 publications found
- 80% were collaborations with McGill
- Noone has published code

Tazare et al. (2022)

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Active comparator new-user (ACNU) cohort design

- Problems avoided by the ACNU design:
  - Confounding by indication (inactive comparator)
  - Healthy adherer bias (prevalent users)

PNUC design in context

Increasingly restrictive ↓

No-use	**Traditional no use**
	No use episodes
Active-comparator	**Generalized prevalent new user**
	Prevalent new user
	Hierarchical prevalent new user
	Active comparator new user

Wintzell et al. (2022)

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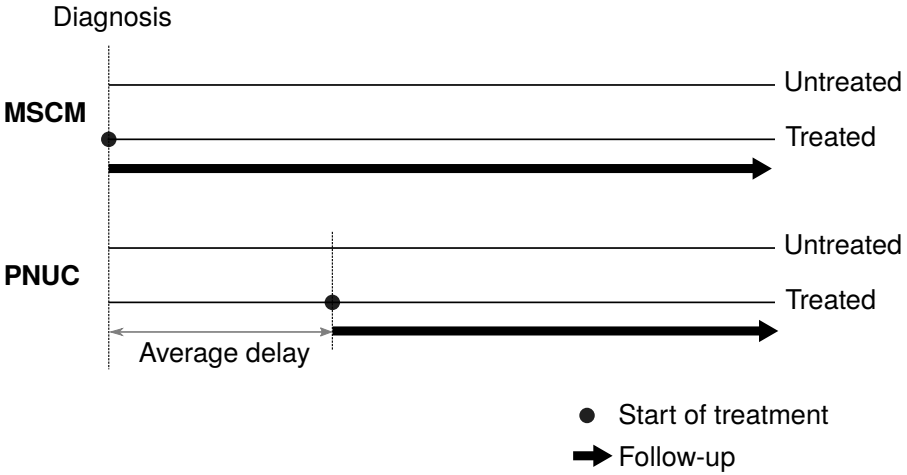
PNUC vs MSM

	PNUC	MSM
Complexity	Higher	Lower
Computation	Higher	Lower
Precision	Higher?	Lower?

Webster-Clark et al. (2022)

Estimands


Diagnosis
MSCM
Untreated
Treated
PNUC
Untreated
Treated
Average delay
Start of treatment
Follow-up

Prevalent new-user cohort design step by step

1. Defining the base cohort
2. Forming exposure sets
3. Estimating the propensity score
4. Matching and forming the analysis cohort
5. Estimating the causal effect

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Defining exposure sets and estimating the propensity score

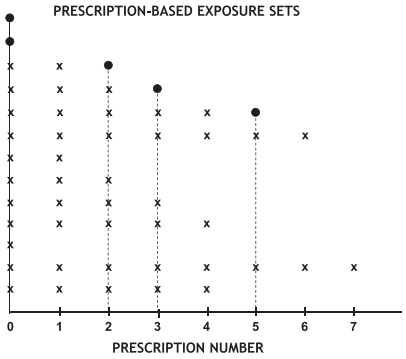

Figure 3. Depiction of a base cohort formed of 13 subjects with prescription-based exposure sets defined by the number of comparator drug prescriptions (**x**) before the first study drug prescription (●) was given

Suissa et al. (2017)

Time-conditional propensity score

- Measured at treatment time
- Positivity verified within exposure set
- Score from conditional logistic regression or Cox
- Prevalent users can fall into multiple exposure sets

Matching

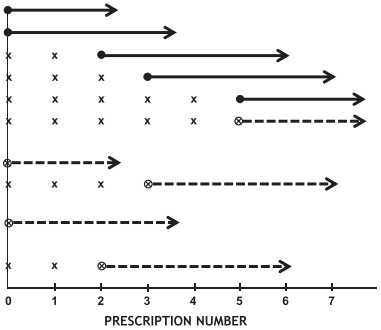

Figure 4. Depiction of the final prevalent new-user comparative cohort with comparator drug subjects matched to study drug subjects on the number of comparator drug prescriptions (x) before the first study drug prescription (●) was given, with the arrows indicating the follow-up period for outcomes

Suissa et al. (2017)

Informative censoring among comparator group

- Follow-up of comparator group is censored if study treatment starts
- Starting treatment = patient is still alive (but sicker?)
- Remove bias through inverse probability of censoring weights (IPCW)

Example study

Practice of Epidemiology

Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis

Tanja Tran and Samy Suissa*

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Initially submitted March 26, 2020; accepted for publication October 27, 2020.

- T. Tran and S. Suissa. **Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis.** *American Journal of Epidemiology*, 190(5):928–938, May 2021. doi:10.1093/aje/kwaa242.

What is the paper about?

- Question: Are PPIs efficacious in idiopathic pulmonary fibrosis?
- Data: UK linked GP and hospital data (CPRD-GOLD/HES/ONS), $n = 2944$
- Outcomes: All-cause mortality, respiratory death, hospitalisation
- Covariates: Demographics, comorbidity, medicines (all time-varying)
- Compare results from three different study designs

Idiopathic Pulmonary Fibrosis (IPF)

- Progressive scarring of the lungs, cause unknown
- Average life expectancy after diagnosis about four years
- Pirfenidone (2008) and nintedanib (2014) slow progression
- Proton pump inhibitors also guideline recommended (weak evidence)
- Contention: PPI effects seen in earlier studies are due to bias

Results

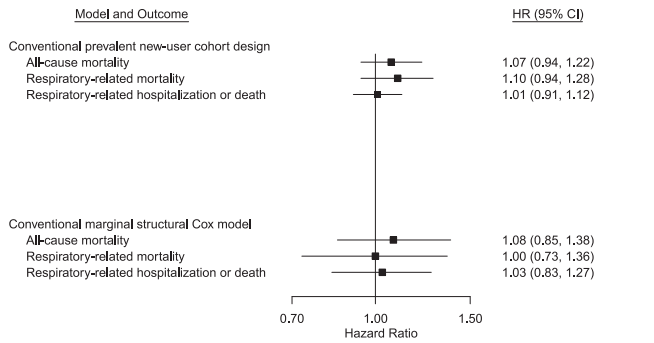

Figure 3. Hazard ratios (HRs) for respiratory-disease–related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence intervals (CIs).

PNUC sub-cohorts

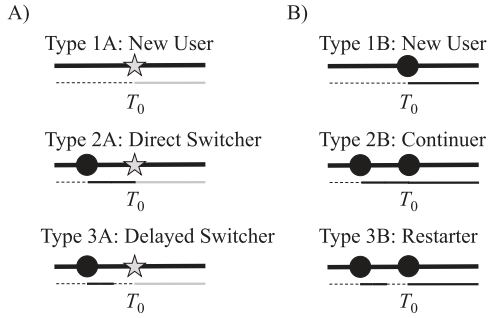

Figure 1. Infographic showing treatment histories of various types of initiators of treatment A and users of B. Panel A includes the initiators of treatment A (types 1A–3A) and panel B includes the 3 corresponding individuals taking treatment B that would be "ideal" counterfactual contrasts for types 1A–3A. Gray stars represent prescriptions for A, while black circles represent prescriptions for B. Below each set of prescriptions is a secondary timeline showing time with no treatment (dashed black), time treated with A (gray), and time treated with B (solid black).

Webster-Clark et al. (2021)

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Developments

- Matching with/without replacement or weighting
- How to condition on “length of exposure”?
- Positivity and matching
- Estimating the propensity score
- Discontinuation only; intensification

Webster-Clark (2020)

Discussion

- Does the PNUC design look useful to you?
- Would you use it rather than a marginal structural model?
- What are the barriers to using these methods?

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Acknowledgments

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