

MI-CRE Methods Group journal club: Prevalent new-user cohort design

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Talk outline

- Paper background
- Prevalent new-user cohort method in detail
- Adjusting for informative censoring
- Results
- What does the PNUC method estimate?
- Loose ends

Introduction

- Question: Are PPIs efficacious in idiopathic pulmonary fibrosis?
- Contention: Effects seen in earlier studies are due to bias
- 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)

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)

Review: Active comparator new-user cohort design

- Confounding by indication (inactive comparator)
- Healthy adherer bias (prevalent users)

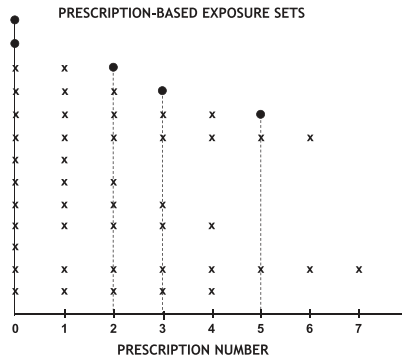
Why *prevalent* new-user?

- *i.e.* Compare those staying on old tx with switchers to new
- Increase sample size if few treatment-naïve patients
- Better external validity e.g. disease progression
- Key feature: conditioning on length of exposure

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

Defining exposure sets and estimating the propensity score



Matching

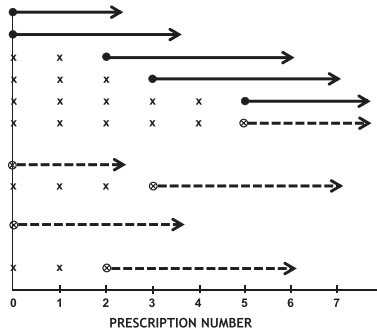


Figure 4. Depiction of the final prevalent new-user comparative cohort with comparator drug subjects matched to study drug subjects on the number of comparator drug prescriptions (x) before the first study drug prescription (●) was given, with the arrows indicating the follow-up period for outcomes

Suissa et al. (2017)

Informative censoring

- In this study, “prevalent user” = IPF patient *not* treated with PPI
- Follow-up of prevalent users is censored if PPI treatment starts
- Starting PPI = patient is still alive (but sicker?)

Adjusting for informative censoring

- Option 1: Restriction
 - exclude PPI ever users from prevalent cohort
- Option 2: Weighting
 - use inverse probability of censoring weights (IPCW)
 - estimate from logistic regression model (*à la* propensity)

Results 1

936 Tran and Suissa

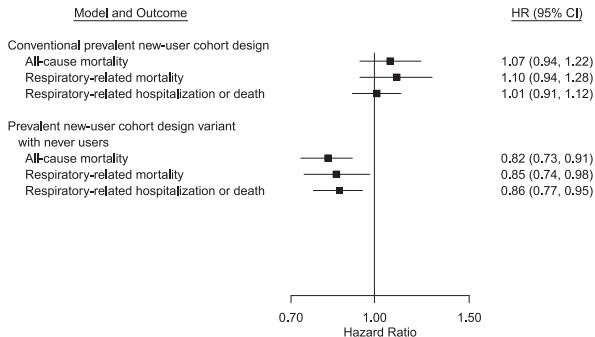


Figure 3. Hazard ratios (HRs) for respiratory-disease-related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence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

Marginal Structural Cox Model

- All patients followed from IPF diagnosis
- Exposure and covariates assessed in each person-month
- Inverse probability of treatment weights (IPTW)
- Inverse probability of censoring weights (IPCW)
- Estimation with weighted time-dependent Cox model

Results 2

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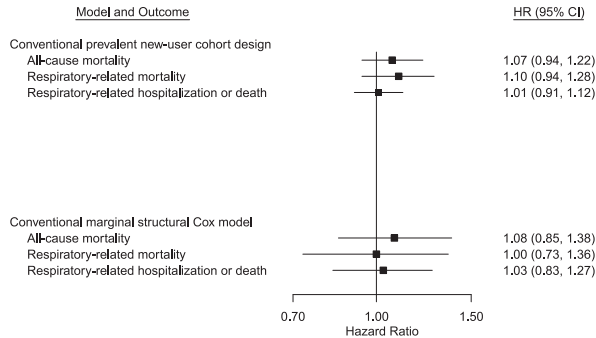
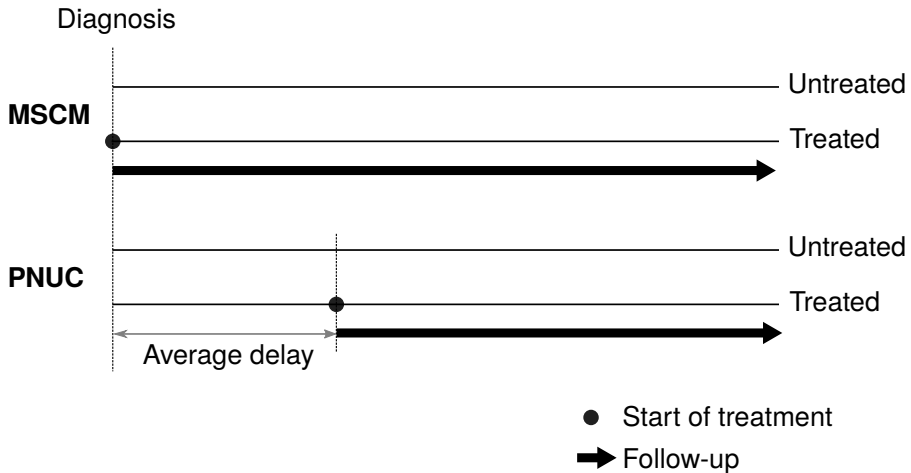


Figure 3. Hazard ratios (HRs) for respiratory-disease-related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence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

Estimands



PNUC sub-cohorts

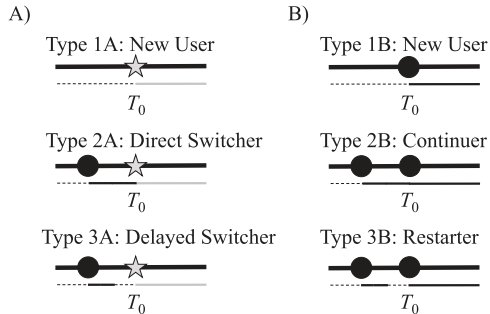


Figure 1. Infographic showing treatment histories of various types of initiators of treatment A and users of B. Panel A includes the initiators of treatment A (types 1A–3A) and panel B includes the 3 corresponding individuals taking treatment B that would be “ideal” counterfactual contrasts for types 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. (2020)

Loose ends

- Sampling with/without replacement
- Conditioning on length of exposure vs entire history
- Positivity and matching
- Estimating the propensity score
- See also: https://pharmacoepi.unc.edu/wp-content/uploads/sites/6788/2020/12/Webster-Clark_Michael_PNU.pdf

Discussion

- Have you used the prevalent new-user cohort design or the marginal structural Cox model approach? If so, please tell us about it.
- Would you use either of these methods for your current research interests? What do you see as the barriers to using them?

Other business

- Suggestions for articles or topics to discuss
- Volunteers to present
- Comments on format, timing, frequency and audience for the journal club

References

- S. Suissa, E. E. M. Moodie, and S. Dell’Aniello. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiology and Drug Safety*, 26(4):459–468, 2017. doi: 10.1002/pds.4107. URL <https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4107>.
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- M. Webster-Clark, R. K. Ross, and J. L. Lund. Initiator Types and the Causal Question of the Prevalent New-User Design: A Simulation Study. *American Journal of Epidemiology*, page kwaa283, Dec. 2020. doi: 10.1093/aje/kwaa283. URL <https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa283/6043913>.