Estimating the long-term effect of early treatment initiation in Parkinson's disease using observational data

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Early treatment initiation in Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder, whose symptoms are treated using medication therapy in the large majority of patients. The long-term effects of the timing of initiation of PD medication are largely unknown. Both patients and physicians may choose to delay initiation of PD medication (such as Levodopa) for various reasons, including concerns regarding the toxicity of therapy and early development of treatment-related side effects. Large observational PD cohort studies are increasingly available. We want to use available data from these studies to estimate the long-term effect of the duration of the medication therapy early in the disease, to complement the available evidence from RCTs, which are expensive to replicate and may be less representative of the population of interest.

Two main goals:

1. Find out what evidence longitudinal observational data can bring to bear on the question of early medication treatment initiation.
2. Show that causal inference methods that take time-varying confounding into account are essential when estimating such effects.

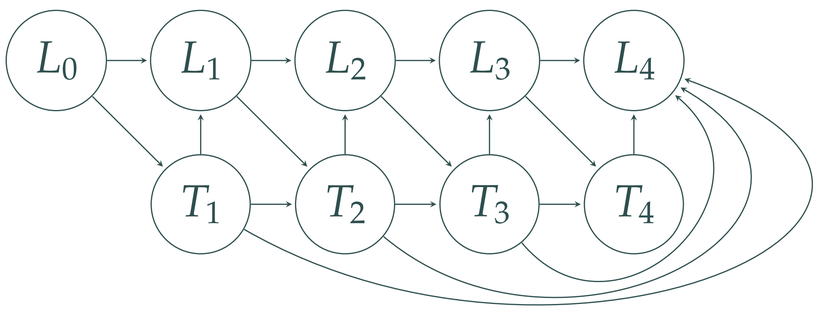
Study Design and Data

The effect estimate of interest is the **effect of the duration of PD medication therapy within the first two years of follow-up, on outcomes at year 2, 3 and 4**. We use data from the Parkinson's Progression Markers Initiative, which gathered data on 423 de novo patients, with a follow-up of up to 8 years. For this analysis, we used:

- 302 patients who started and did not stop using PD medication;
- Bi-annual visits during the first two years (5 visits);
  - Covariates for adjustment: age, education, time of diagnosis, MDS-UPDRS ratings, MoCA, MSEADL;
- Outcome measurements at year 2, 3 and 4;
  - Main: MDS-UPDRS Part III subscore (movement);
  - Secondary: Schwab & England Activities of Daily Living scores and ratings for side-effects.

Time-varying Confounding

We want to estimate what the effect of early treatment initiation is. However, treatment initiation is influenced by the current disease state: patients who are doing worse are more likely to start treatment. At the same time, the decision whether to initiate treatment affects the disease state at the next time point. These effect occur not just at baseline, but at every subsequent time-point. This is known as time-varying confounding (treatment-confounder feedback) and we need to adjust for it to correctly estimate the effect of the intervention of changing the start of treatment.



Methods

Simple Adjustment

For comparison we consider a model that does not adjust for confounding, and returns a linear model of treatment duration on outcomes. A slight extension of this model also adjusts for the outcome at baseline.

$$y = \beta_0 + \gamma \cdot \frac{\text{sum}(\bar{t})}{2} + \beta_1 y_0$$

Inverse Probability of Treatment Weighting

To adjust for time-varying confounding we weight the observations by the inverse of the probability of the treatment choice at each visit (normalized by the prior probability of the treatment), modelled using logistic regression models at each time-point.

$$w = \prod_{k=1}^{4} \frac{f(t_k|t_{k-1})}{f(t_k|l_{k-1}, t_{k-1})}$$

Parametric g-formula

We simulate the disease progression of all patients under different treatment regimes, and summarize the resulting outcomes using a marginal structural model. The disease progression at each time-point is modelled using linear regression models, taking into account the measurement history as covariates.

$$f(y|\bar{t}, \bar{l}) \prod_{k=0}^{4} f(l_k|\bar{l}_{k-1}, \bar{t}_k)$$

Results

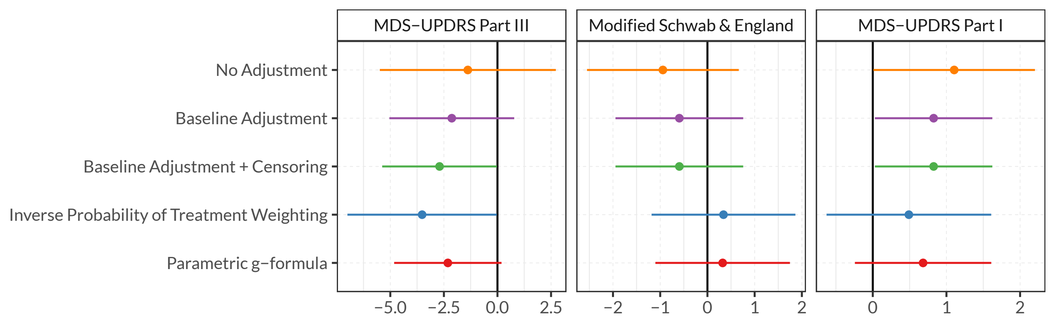


Figure 1: Effect of an additional year of PD medication therapy on outcomes after two years estimated using different methods. Intervals indicate ±2 times the standard deviation of the estimator, estimated using 1000 bootstrap replicates. For Modified Schwab & England, higher scores correspond to improved disease outcomes, while for MDS-UPDRS part I and III, lower scores correspond to more beneficial outcomes. Note that adjusting for more of the confounding effects shifts the estimates to more beneficial outcomes for all three measures, indicating the importance of using these types of methods when analyzing this data.

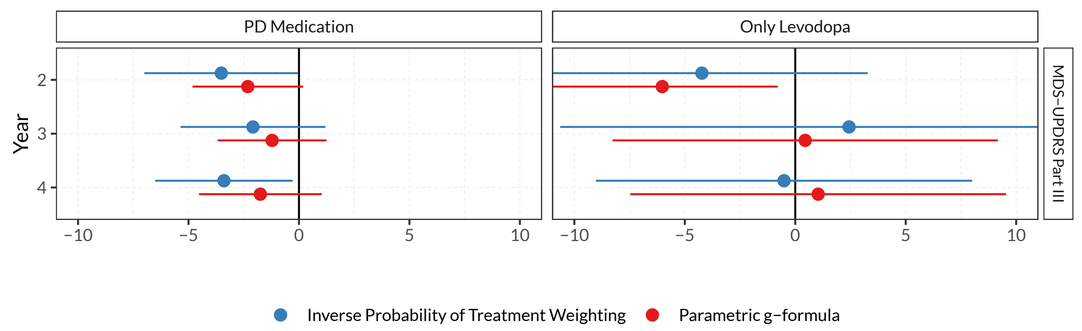


Figure 2: Effect of one year of PD medication respectively Levodopa treatment ($n = 82$) during the first two years of follow-up. Effect on MDS-UPDRS part III subscore measured at year 2, 3 and 4, for inverse probability of treatment weighting and the parametric g-formula. Lower scores correspond to better disease outcomes. Intervals indicate ±2 times the standard deviation of the estimator, estimated using 1000 bootstrap replicates.

Conclusions

1. Adjusting for time-varying confounding is important when studying interventions that happen over time.
2. We find no evidence for worse outcomes and tentative evidence for beneficial effects of early treatment initiation for our main outcome of interest.
3. We find no evidence of worse, nor improved secondary outcomes, due to high uncertainty in the estimates.