Item-Response Theory to Adjust Proxy-Responses when Evaluating Treatment Effects in Quality-of-Life Outcomes: an Application to Parkinson's Disease

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Overview

In this study, we utilized data from a recent comparative effectiveness trial for patients with Parkinson's disease to compare novel item-response theory-based methods to prior methods for adjusting proxy-responses when estimating treatment effects on Quality-of-Life outcomes.

Background

- Parkinson's disease (PD) is the fastest growing neurological disorder in terms of prevalence, disability, and death
- Treatments such as palliative care (PC) have become an important part of PD management to improve patient quality-of-life (QoL)
- High rates of dementia and cognitive impairments among patients with PD can be problematic when evaluating self-reported outcomes such as QoL
- When patients are unable to self-report, a proxy can respond on the patient's behalf but including these responses in analyses can introduce bias
- No prior studies have addressed how inclusion of proxy-reported data influences treatment effects in clinical trials
- Aim: this study proposes utilizing novel item-response theory-based methods to adjust proxy responses when evaluating treatment effects and compares it against prior methods

Methods

- Data were utilized from a recent comparative effectiveness trial assessing whether PC training improved QoL in patients with PD in comparison to standard care (N=305)
- Outcome: 13-item Quality of Life in Alzheimer's disease (QoL-AD) scale at 6-month follow-up
- Proxy-reported values were adjusted using the following methods:

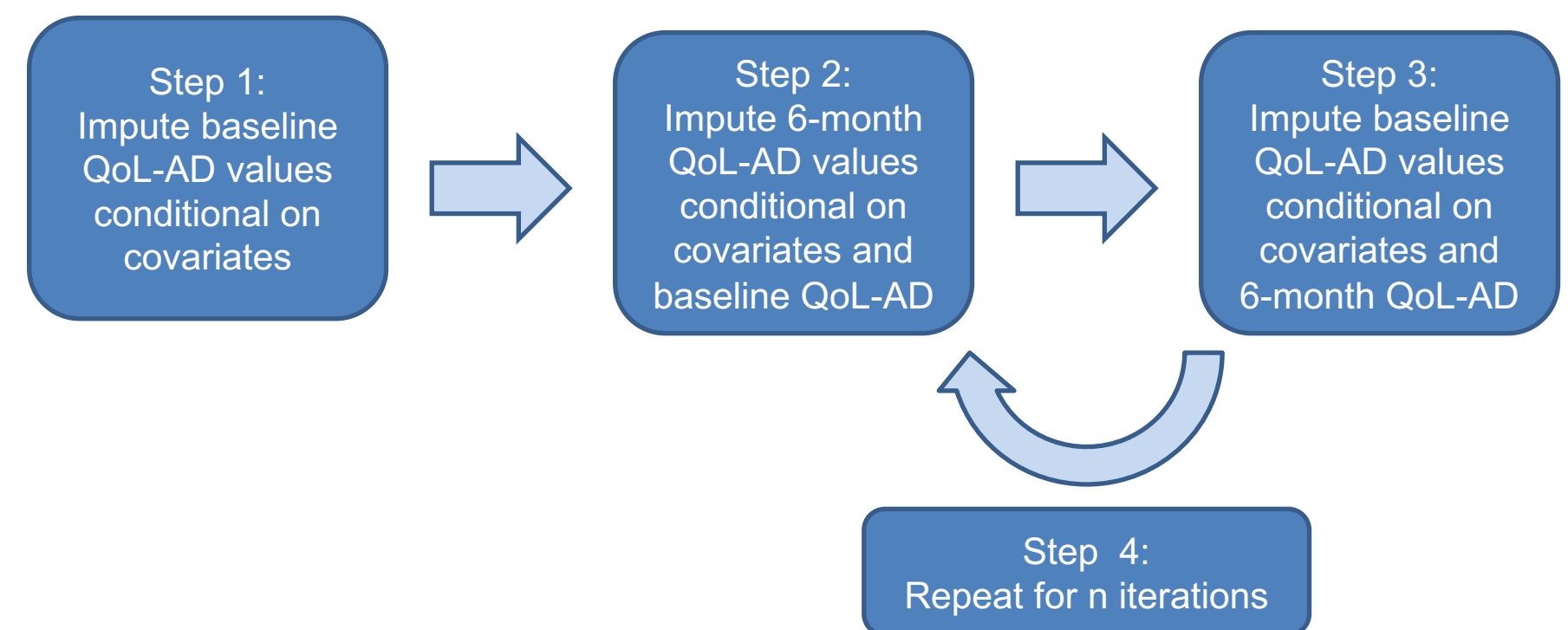| Method	Description
Substitution	Impute proxy responses directly as self-report
Regression Prediction	Fit linear model using self-report data adjusting for covariates. Use model estimates to predict QoL values for proxy-reports.
Predictive Mean Matching (PMM)	Fit linear model using self-report data adjusting for covariates and use model estimates to predict outcome values for all patients. Then, match proxy respondents to self-report individuals using nearest neighbor matching based on predicted outcome values. The matched self-report values are used to impute the proxy-responses.
IRT with Latent Regression	Same process as PMM but uses 2-PL model instead of linear model

- The multilevel 2-Parameter logistic (2-PL) IRT model allows for item level analysis of QoL items:

$$logit(p_{ik}) = \alpha_k(\theta_i - \beta_k)$$

- θ_i is the ability of patient i
- α_k is the discrimination of item k
- β_k is the severity of item k
- p_{ik} is the probability of patient i endorsing item k

MICE

- Multiple imputation using chained equations (MICE) was utilized within the imputation-based methods to account for the correlated nature of the repeated QoL-AD measurements

Step 1: Impute baseline QoL-AD values conditional on covariates → **Step 2:** Impute 6-month QoL-AD values conditional on covariates and baseline QoL-AD → **Step 3:** Impute baseline QoL-AD values conditional on covariates and 6-month QoL-AD

Step 4: Repeat for n iterations

- Next, fit a linear mixed effects model on the final imputed data set to estimate between- and within-group treatment effects on QoL-AD using difference in differences
- Repeat this process for m imputations

Results

- 18% of baseline and 37% of 6-month follow-up QoL-AD values were proxy-reported. These proportions were similar between treatment groups

Within treatment group change from baseline:
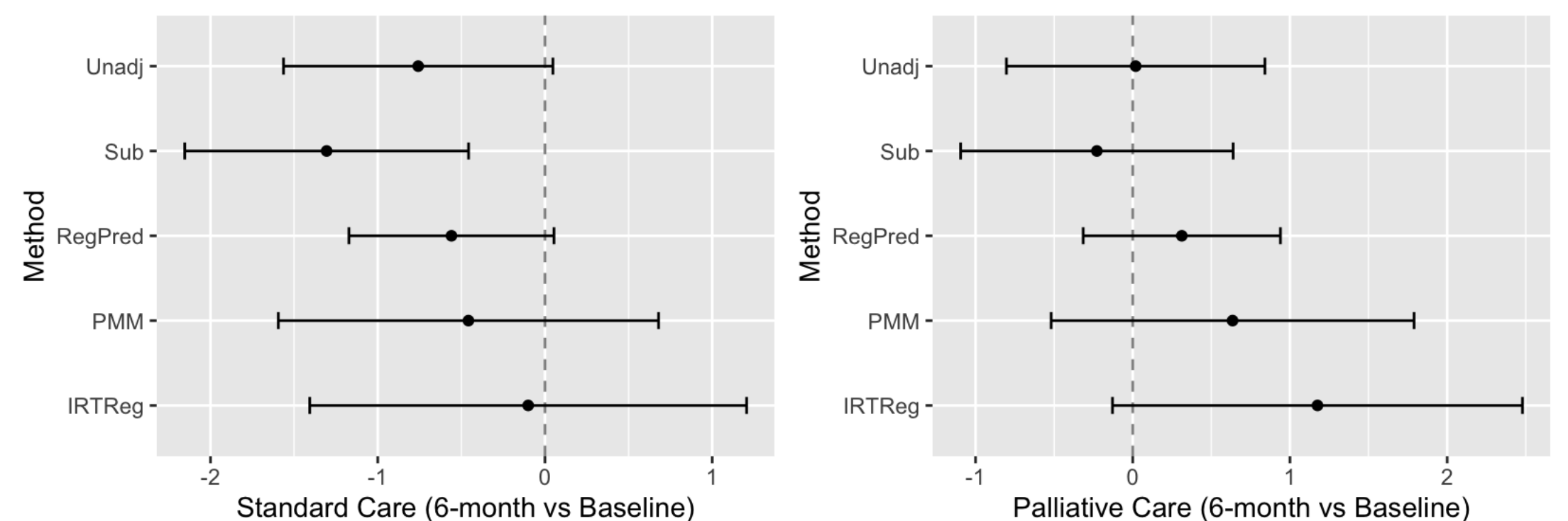
- Within the standard care group, substitution found a significant decrease in QoL-AD, whereas this effect was smaller in magnitude and not significant for all other methods
- Within the PC group, IRT had the largest positive change in QoL-AD; however, with the largest standard error, this change was not significantly different than zero, nor was this effect significant for the remaining methods

Between group change from baseline:
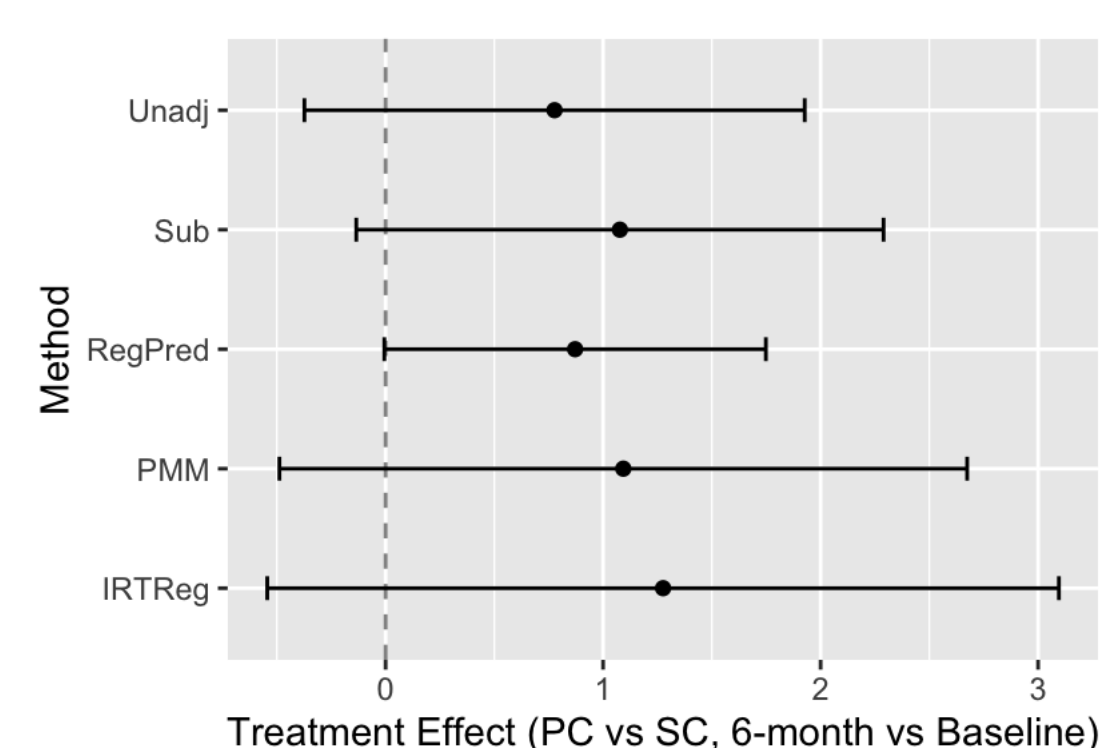
- At 6 months, there were no significant treatment effects between groups on QoL-AD for any of the methods at the 5% alpha level

Conclusion

- Direct use of proxy-reported values in methods such as substitution can lead to underreporting of QoL-AD, whereas imputation-based methods utilizing IRT can provide better estimates of the variability of the treatment effects
- The method selected can impact both the direction and magnitude of treatment effects and can therefore have significant implications on research findings making it an important consideration when analyzing clinical data

References

Kluger, B.M., Katz, M., Galifianakis, N.B., Pantilat, S.Z., Hauser, J.M., Khan, R., Friedman, C., Vaughan, C.L., Goto, Y., Long, S.J., Martin, C.S., Dini, M., McQueen, R.B., Palmer, L., Fairclough, D., Seeberger, L.C., Sillau, S.H., Kutner, J.S. (2024). Patient and Family Outcomes of Community Neurologist Palliative Education and Telehealth Support in Parkinson Disease. JAMA Neurol, 81(1):39-49.