Simple methods for the estimation and sensitivity analysis of principal strata effects using marginal structural models: application to a bone fracture prevention trial

Introduction

In randomized clinical trials, it is often of interest to estimate the treatment effects on quality of life (QOL), in addition to those on the event itself. When an event occurs for some patients before the QOL score is measured, investigators may compare QOL scores in subgroups of patients defined by the event after randomization. However, owing to a post-randomization selection bias, this analysis can mislead about treatment efficacy. To address this issue, the principal stratification framework was proposed (Frangakis & Rubin, 2002). Principal strata refer to subgroups of the individuals stratified by the potential intermediates that they would have had if they had been assigned to each arm of the study (Hernan et al, 2004). Treatment effects estimated within the principal strata are sometimes referred to as principal strata effects (PSEs). Unfortunately, we do not know who is in each principal stratum, because if a subject experienced the event under the treatment arm, it is unclear whether that subject would have experienced the event under the control arm. Therefore, we cannot estimate PSEs directly from the observed data. Although several researchers have discussed methods for the estimation and sensitivity analysis of PSEs (Gilbert et al, 2003) (Hyden et al, 2005) (Chiba, 2011), most have complex mathematical forms that may be difficult to implement in practice.

Objection and Method

We intelligibly describe a simple procedure for estimating the PSEs using marginal structural models. In addition, we present a simple sensitivity analysis method for examining the resulting estimates. These methods are applied to the recent Japanese Osteoporosis Intervention Trial (JOINT-02), which compared the benefits of a combination therapy with those of a monotherapy in terms of fracture prevention.

Results and Discussion

We described a simple procedure for estimating PSEs using MSMs under two assumptions: a monotonicity assumption and an assumption of no unmeasured confounder for the mediator-outcome relationship. We also presented a simple sensitivity analysis method for when the second assumption is relaxed. Further, we used the data from JOINT-02, a randomized clinical trial for fractures, to demonstrate that these methods can easily be implemented in practice. The PSEs for the subgroups unfractured irrespective of treatment status and fractured irrespective of treatment status was estimated, and the estimated PSEs showed a larger combination treatment effect compared with the monotherapy treatment effect than the estimated crude treatment effect.

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