Treatment of randomly censored covariates in Alzheimers disease studies

https://www.neurodegenerationresearch.eu/survey/treatment-of-randomly-censored-covariates-in-alzheimers-disease-studies/

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Research Abstract

SUMMARY The problem of censored covariates arises frequently in family history studies, in which an outcome of interest is regressed on an age of onset, as well as in longitudinal cohort studies in which biomarkers may be measured post-baseline and it may be necessary to adjust

for duration of disease. We have encountered several Alzheimer's disease (AD) research questions within the Harvard Aging Brain Study (HABS) and the National Alzheimer's Coordinating Center (NACC) cumulative database . These studies seek to understand the role of family history, which requires adjustment for parental age of onset of dementia, and the pathological progression of AD, which requires adjustment for duration of cognitive impairment. Both age of onset and duration of disease are incompletely observed (i.e., censored). Use of censored covariates without any adjustment is well known to lead to bias in estimates of the coefficients of interest and inflated type I error. Although there is extensive literature on methods for analysis of censored outcomes, there is a very limited literature that addresses the problem of randomly censored covariates within regression models; existing literature deals almost exclusively with censoring due to fixed limits of detection. The complete-case approach, which deletes the observations that have a censored covariate, can be highly inefficient with moderate censoring, such as may arise in family studies with an age of onset covariate. We propose two threshold methods for linear and generalized linear regression models with covariate subject to random censoring. The primary approach is called deletion threshold regression. The secondary approach is called complete threshold regression. These methods are appealing for their conceptual simplicity, their validity for estimation and hypothesis testing and their efficient using of the data.We also propose a reverse survival regression approach as an alternative to test the significance of the effect of the censored covariate. In Aim 1, we develop two methods of threshold regression and justify the test based on reverse survival regression. In Aim 2, we evaluate the proposed methods of threshold regression in simulation. In Aim 3, we apply the proposed methods of threshold regression to four Alzheimer's studies. In Aim 4, we develop publicly available software on the two threshold regression methods. In summary, our proposed theoretical and software developments, along with our extensive simulation studies, will jointly serve to remove a major barrier to valid and practical analyses of family history studies, longitudinal biomarker studies and studies adjusting for duration of disease in Alzheimer's and other diseases.

Further information available at:

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