

Statistical analysis of longitudinal psychiatric data with dropouts

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Abstract

Longitudinal studies are used in psychiatric research to address outcome changes over time within and between individuals. However, because participants may drop out of a study prematurely, ignoring the nature of dropout often leads to biased inference, and in turn, wrongful conclusions. The purpose of the present paper is: (1) to review several dropout processes, corresponding inferential issues and recent methodological advances; (2) to evaluate the impact of assumptions regarding the dropout processes on inference by simulation studies and an illustrative example using psychiatric data; and (3) to provide a general strategy for practitioners to perform analyses of longitudinal data with dropouts, using software available commercially or in the public domain. The statistical methods used in this paper are maximum likelihood, multiple imputation and semi-parametric regression methods for inference, as well as Little's test and index of sensitivity to nonignorability (ISNI) for assessing statistical dropout mechanisms. We show that accounting for the nature of the dropout process influences results and that sensitivity analysis is useful in assessing the robustness of parameter estimates and related uncertainties. We conclude that recording the causes of dropouts should be an integral part of any statistical analysis with longitudinal psychiatric data, and we recommend performing a sensitivity analysis when the exact nature of the dropout process cannot be discerned.

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1. Introduction

Longitudinal studies are widely used in psychiatric research to measure treatment outcomes over time within individuals as well as changes across these individuals. Despite the collection of multiple, repeated measurements over time in most longitudinal studies, some analyses use only baseline and endpoint values comparing pre-post changes across different groups by analysis of variance (ANOVA) or analysis of covariance (ANCOVA) methods.

In such analyses, data are not utilized efficiently since measurements between the baseline and the endpoint are ignored. When endpoint values are not available due to dropouts, analysis with only complete cases and a traditional method called “last observation carried forward” (LOCF) are commonly practiced (Mallinckrodt et al., 2003). LOCF analysis uses all subjects and imputes the missing values with the last observed value, a method that assumes that the outcomes would not have changed from the last observed value. This assumption of constant profile after dropout is hard to justify in many treatment trial settings.

Random regression models (Gibbons et al., 1993) provide a powerful tool for analyzing longitudinal data. In statistical analysis, these models are also referred to as mixed

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effects regression models, mixed effects models, or multi-level models. Over the last decade, these models have been used frequently in the psychiatric literature (Mazumdar et al., 2002; Hedeker, 2003; Houck et al., 2004). These models use all the data that are collected longitudinally and also account for within-subject correlation. However, the use of random regression models can lead to invalid conclusions when data are not missing at random (Little and Rubin, 2002; Rubin, 1976); that is, when the reason for a subject to drop out depends on the underlying value of the unobserved outcome even given recorded data from that subject. The assumption of missing at random may not be correct in psychiatric studies because participants may drop out of the study prematurely because of treatment failure, side effects, or unwillingness to comply with the treatment protocol. In psychiatric studies, “respondent burden” that may arise from many visits and assessments is frequently seen to be a reason for noncompliance with study procedures, leading to withdrawal from the study. Unfortunately, investigating the causes of dropout as an integral part of data analysis is not yet a well established practice.

Various features of, and appropriate statistical analyses for, longitudinal data with dropouts have been reviewed and discussed in the statistical literature (Little, 1995). A recent tutorial article for handling dropouts in longitudinal studies was designed to synthesize and illustrate the broad array of techniques used to address outcome-related dropout mechanisms, with an emphasis on regression based methods (Hogan et al., 2004). Another report discussed progress in analyzing repeated measures data (Gueorguieva and Krystal, 2004) and concluded that repeated-measures ANOVA still continues to be used widely despite both problematic interpretation and the availability of other methods. They recommended mixed effects models as the preferred choice for the analysis of such data due to both their greater flexibility in modeling time effects or in properly accounting for correlation between repeated measurements and their ability to handle missing data more appropriately. The authors noted, however, that mixed effects models can give biased results in the presence of missing values that are missing not at random (MNAR). They concluded that specific guidelines for the use of various methods for analyzing data from clinical trials and longitudinal follow-up studies in psychiatry are not yet available.

Molenberghs et al. provided a comprehensive summary of modeling frameworks and methods for analyzing incomplete longitudinal clinical trial data in circumstances where data may be MNAR (Molenberghs et al., 2004). Schafer and Graham argued that since these analyses are problematic, it is unwise to blindly shift to such methods, just as it can be dangerous to ignore nonrandom mechanisms altogether (Schafer and Graham, 2002). They suggested the use of sensitivity analysis, a procedure to ascertain how a given model output depends upon the input parameters (Saltelli et al., 2002). This is a powerful

paradigm for assessing the robustness and reliability of a fitted model.

Recent papers on longitudinal data analysis do not adequately address the needs of practitioners involved in psychiatric research to understand different dropout processes, associated inferential issues, and the limitations of software available commercially or in the public domain. Although the models and the issues to be discussed are relevant to clinical trial data well beyond psychiatry, the specific application to psychiatric trials is of particular importance. In psychiatric trials, there are a wide range of reasons for dropout, including side effects, feeling better or feeling worse, onset of other psychiatric disorders, or withdrawal of consent due to a variety of personal reasons, some of which may be attributable to the presence of the psychiatric disorder being treated. These reasons, if not recorded as part of the observed data in the study, can lead to MNAR data, a possibility that should be considered in any psychiatric clinical trial.

Thus, in this article we describe several dropout processes and the associated inferential issues in non-technical language, and we present a general conceptual and statistical analytic framework in which these procedures can be followed to provide sensible conclusions. Although psychiatric studies may include continuous and/or discrete outcomes, we consider only analytic methods pertaining to continuous outcome measures in order to focus the paper. We note that some of the methods discussed here can be extended to discrete data.

We illustrate these procedures with data from a longitudinal psychiatric clinical trial. We use simulation studies to demonstrate what may happen in the inferential domain if the underlying assumptions pertaining to a chosen method are not satisfied. We conclude with practitioner guidelines for analyzing longitudinal data with dropouts.

2. Description of longitudinal data with dropouts

In typical longitudinal psychiatric studies, an outcome variable such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), is recorded repeatedly over time, usually in order to document change with treatment. The longitudinal nature of the resulting data set provides rich information, such as variability of the outcome within an individual, variability of the outcome between individuals, and trend of the outcome over time, as well as effect of treatment on outcome. However, dropouts are inevitable in most studies because some subjects may relocate, become frustrated with the perceived ineffectiveness of the assigned treatment, or experience severe side effects. Hence, the sub-sample with an outcome recorded at any given time may not be a random sample of the complete study population. The observed data set can be regarded as the result of a selection process. Because of potential selection bias, different dropout processes have different implications in terms of appropriate statistical analyses.

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