

# **Estimation of Effects of Endogenous Time-Varying Covariates: A Comparison Of Multilevel Linear Modeling and Generalized Estimating Equations**

PROPOSAL

**Ward B. Eiling (9294163)**

Supervisors: Ellen Hamaker and Jeroen Mulder

*Master's degree in Methodology and Statistics for the Behavioural,  
Biomedical and Social Sciences*

*Utrecht University*

September 28, 2024

Word count: 699

FETC-approved: 24-2003

*Candidate journal: Psychological Methods*

## Introduction

Across a wide range of disciplines, researchers analyze clustered longitudinal, observational data to investigate prospective causal relationships between variables. To analyze such data, the psychological sciences most commonly resort to the multilevel linear model (MLM, [McNeish et al., 2017](#)), which in the context of longitudinal data analysis, separates observed variance into stable between-person differences and within-person fluctuations ([Hamaker & Muthén, 2020](#)). Conversely, other fields, such as biostatistics and econometrics often favour generalized estimating equations for the analysis of longitudinal data (GEE, [McNeish et al., 2017](#)). While some interdisciplinary research has compared these methods ([McNeish et al., 2017](#); [Muth et al., 2016](#); [Yan et al., 2013](#)), these studies do not clarify how both modeling frameworks address different kinds of covariates.

Recent evidence has highlighted an issue present in both methods, where controlling for *time-varying endogenous covariates* may lead to biased causal estimates ([Pepe & Anderson, 1994](#); [Qian et al., 2020](#)). A time-varying covariate is *endogenous* if it is directly or indirectly influenced by prior treatment or outcome, meaning its value may be determined by earlier stages of the process ([Qian et al., 2020](#)). As a result of including these covariates in the mentioned models, ordinary interpretations of the coefficients are no longer valid ([Qian et al., 2020, p. 3](#)). According to [Diggle \(2002\)](#), this issue not only pertains GEE and MLM, but *all* longitudinal data analysis methods. However, due to a divide between the disciplines that employ these methods, such critiques of the MLM appear to have been unable to reach the applied researcher in psychology. One specific reason might be that the technical jargon in other disciplines makes it difficult for researchers to recognize when and how these issues emerge<sup>1</sup>.

---

<sup>1</sup>For instance, the term ‘endogeneity’ in econometrics, while related, has a distinct meaning from that of an endogenous variable, which can sometimes cause confusion.

More specifically, it may be noticed that while the MLM literature emphasizes on the distinction between different centering methods and the effect of cross-level interactions on parameter interpretations, the GEE literature appears to focus more on the marginal and conditional interpretations of model parameters. Through a cross-fertilization of these debates, this project aims to (1) explain the issue of including endogenous covariates in analyses involving GEE, MLM and DSEM (a widely used framework in the social sciences based on MLM) in a psychological context and (2) establish guidelines on how researchers can prevent this issue in their longitudinal data analysis. Accordingly, the following research question will be addressed: *to what extent does the inclusion of endogenous variables in multilevel linear models and generalized estimating equations result in biased estimates?* In line with the literature ([Diggle, 2002](#); [Pepe & Anderson, 1994](#); [Qian et al., 2020](#)), we expect that the inclusion of endogenous time-varying covariates in longitudinal data analyses may result in bias that—depending on the circumstances—can promote the potential for faulty inferences.

## Analytic Strategy

To uncover the undesirable effects of endogenous covariates and investigate robustness against these effects, we will carry out simulations in which data will be generated according to several increasingly complex data generating mechanisms. These scenarios will be visually represented using directed acyclic graphs and analyzed using GEE, MLM and DSEM. We will start out with a scenario of the basic MLM—where a time-varying outcome  $Y$  is regressed on one time-varying predictor  $X$  and in the presence of stable between person differences in the intercept—and increase the complexity until we reach the scenario that includes a time-varying endogenous covariate. The primary interest of this simulation study is the comparative performance in terms of bias for the estimation of the effect of  $X$  to  $Y$  and the secondary interest is the efficiency in mean squared error (MSE). We consider varying number of time points and sample sizes.

Statistical analyses pertaining to the GEE and basic MLM will be performed in R, version 4.2.0 ([R Core Team, 2022](#)). To fit the GEE, the R-packages `geepack` ([Halekoh et al., 2006](#)) and `gee` ([Carey et al., 2024](#)) will evaluate several different working correlation structures, including independent, exchangeable, AR(1) and unstructured. To fit the basic MLM, the R-package `lme4` ([Bates et al., 2015](#)) will be employed, where we will both evaluate restricted maximum likelihood estimation and ordinary maximum likelihood estimation. Extensions of the MLM from the DSEM framework will be fitted using `Mplus`, version 8.10 ([Muthén & Muthén, 1998](#)).

## References

- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, 67(1), 148. <https://doi.org/10.18637/jss.v067.i01>
- Carey, V. J., and 4.4), T. S. L. (R. port of versions 3. 13., src/d\*), C. M. (LINPACK. routines in, & updates), B. R. (R. port of version 4. 13. and. (2024). *Gee: Generalized estimation equation solver*. <https://cran.r-project.org/web/packages/gee/index.html>
- Curran, P. J., & Bauer, D. J. (2007). Building path diagrams for multilevel models. *Psychological Methods*, 12(3), 283–297. <https://doi.org/10.1037/1082-989X.12.3.283>
- Diggle, P. (2002). *Analysis of Longitudinal Data*. OUP Oxford.
- Drikvandi, R., Verbeke, G., & Molenberghs, G. (2024). A framework for analysing longitudinal data involving time-varying covariates. *The Annals of Applied Statistics*, 18(2), 1618–1641. <https://doi.org/10.1214/23-AOAS1851>
- Erler, N. S., Rizopoulos, D., Jaddoe, V. W., Franco, O. H., & Lesaffre, E. M. (2019). Bayesian imputation of time-varying covariates in linear mixed models. *Statistical Methods in Medical Research*, 28(2), 555–568. <https://doi.org/10.1177/0962280217730851>
- Greenland, S., Pearl, J., & Robins, J. M. (1999). Causal diagrams for epidemiologic research. *Epidemiology*, 10(1), 37–48. <https://www.jstor.org/stable/3702180>
- Halekoh, U., Højsgaard, S., & Yan, J. (2006). The r package geepack for generalized estimating equations. *Journal of Statistical Software*, 15/2, 111.
- Hamaker, E. L., & Muthén, B. (2020). The fixed versus random effects debate and how it relates to centering in multilevel modeling. *Psychological Methods*, 25(3), 365–379. <https://doi.org/10.1037/met0000239>

- Kim, Y., & Steiner, P. M. (2021). Causal graphical views of fixed effects and random effects models. *British Journal of Mathematical and Statistical Psychology*, 74(2), 165–183. <https://doi.org/10.1111/bmsp.12217>
- McNeish, D., Stapleton, L. M., & Silverman, R. D. (2017). On the unnecessary ubiquity of hierarchical linear modeling. *Psychological Methods*, 22(1), 114–140. <https://doi.org/10.1037/met0000078>
- Mund, M., Johnson, M. D., & Nestler, S. (2021). Changes in size and interpretation of parameter estimates in within-person models in the presence of time-invariant and time-varying covariates. *Frontiers in Psychology*, 12. <https://doi.org/10.3389/fpsyg.2021.666928>
- Muth, C., Bales, K. L., Hinde, K., Maninger, N., Mendoza, S. P., & Ferrer, E. (2016). Alternative Models for Small Samples in Psychological Research: Applying Linear Mixed Effects Models and Generalized Estimating Equations to Repeated Measures Data. *Educational and Psychological Measurement*, 76(1), 64–87. <https://doi.org/10.1177/0013164415580432>
- Muthén, L. K., & Muthén, B. O. (1998). *Mplus user's guide* (Eight Edition). Muthén & Muthén.
- Pepe, M. S., & Anderson, G. L. (1994). A cautionary note on inference for marginal regression models with longitudinal data and general correlated response data. *Communications in Statistics - Simulation and Computation*, 23(4), 939–951. <https://doi.org/10.1080/03610919408813210>
- Qian, T., Klasnja, P., & Murphy, S. A. (2020). Linear mixed models with endogenous covariates: Modeling sequential treatment effects with application to a mobile health study. *Statistical Science : A Review Journal of the Institute of Mathematical Statis-*

*tics*, 35(3), 375–390. <https://doi.org/10.1214/19-sts720>

R Core Team. (2022). *R: A language and environment for statistical computing*. <https://www.R-project.org/>

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical Linear Models: Applications and Data Analysis Methods* (2nd ed.). SAGE.

Robins, J. M., Hernán, M. Á., & Brumback, B. (2000). Marginal structural models and causal inference in epidemiology. *Epidemiology*, 11(5), 550. [https://journals.lww.com/epidem/fulltext/2000/09000/marginal\\_structural\\_models\\_and\\_causal\\_inference\\_in.11.aspx](https://journals.lww.com/epidem/fulltext/2000/09000/marginal_structural_models_and_causal_inference_in.11.aspx)

Wodtke, G. T. (2020). Regression-based adjustment for time-varying confounders. *Sociological Methods & Research*, 49(4), 906–946. <https://doi.org/10.1177/0049124118769087>

Yan, J., Aseltine, R. H., & Harel, O. (2013). Comparing Regression Coefficients Between Nested Linear Models for Clustered Data With Generalized Estimating Equations. *Journal of Educational and Behavioral Statistics*, 38(2), 172–189. <https://doi.org/10.3102/1076998611432175>