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

Research Report

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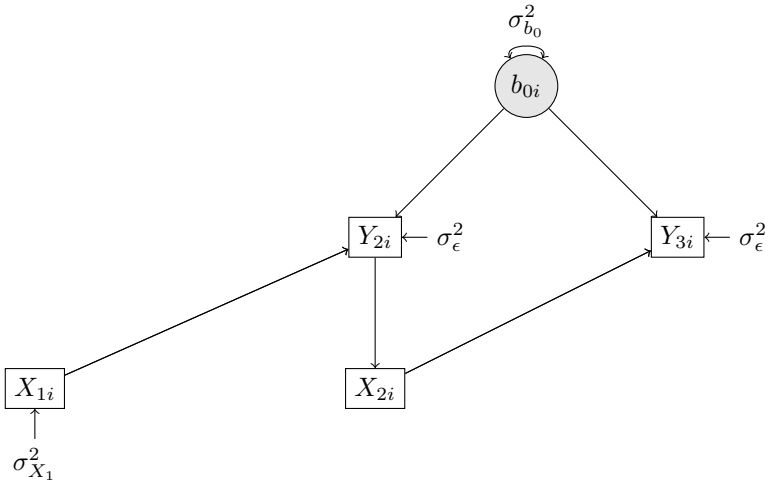
1 Introduction

Across a wide range of disciplines, researchers analyze clustered longitudinal, observational data to investigate prospective causal relationships between variables. When analyzing 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 (GEE) for the analysis of longitudinal data (McNeish et al., 2017). Despite some cross-disciplinary efforts to compare these methods (McNeish et al., 2017; Muth et al., 2016; Yan et al., 2013), their scarcity may leave researchers with limited guidance in choosing the most suitable approach for their application.

A recent study by Qian et al. (2020) highlighted an issue present in both methods—except for GEE with working independence—where controlling for *time-varying endogenous covariates* may lead to biased causal estimates. 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). Figure 1 showcases a time-varying endogenous covariate X_{it} in the context of a simple multilevel linear model with a random intercept b_{0i}. As a result of including these covariates in these models, ordinary interpretations of the coefficients are no longer valid (Qian et al., 2020, p. 3).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.

Figure 1: Multilevel Linear Model with Time-Varying Endogenous Covariate X_{it}.



Note. Adapted from Section 2.2 of Qian et al. (2020).

However, due to a divide between the disciplines that employ these methods, such critiques of the MLM appear to have largely failed 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[^1]. Therefore, this report aims to understand and explain the issue of including endogenous covariates in analyses involving GEE and MLM in a psychological context. To achieve this aim, the current investigation employs (a) graphical tools such as the directed acyclic graph (DAG) and path diagram to assess potentially relevant assumptions, as well as (b) data simulations with additional scenarios to pinpoint the issue. Accordingly, the following research questions will be addressed:

(1) When does the inclusion of endogenous variables in multilevel linear models result in biased estimates of the treatment effect?

(2) When does the inclusion of of endogenous covariates in multilevel linear models result in a discrepancy between conditional and marginal interpretations of the treatment effect?

2 Methods

To obtain a better understanding of the issue exposed by Qian et al. (2020), two methods were employed. First, graphical methods were used provide insight into the presence and extent of bias with potential violation of assumptions: (a) path diagrams were used to evaluate the conditional independence assumption and (b) directed acyclic graphs (DAGs) were used to evaluate the backdoor criterion (Pearl, 1988, 2009). Second, a simulation study was performed to reproduce the results for the generative models (GMs) from Qian et al. (2020) and to further isolate the issue using additional GMs. In this simulation, bias in the treatment effect (RQ 1) was assessed with analytical multilevel models. The discrepancy between conditional and marginal interpretations of the treatment effect (RQ 2) was assessed with GEE with working independence.

2.1 Data Generation

In the simulation Qian et al. (2020) considered three generative models (GMs), all of which have an endogenous time-varying covariate. In GM1 and GM2, the endogenous covariate X_{it} equals the previous outcome Y_{it} plus some random noise, so the *conditional independence* assumption is valid. In GM3, the endogenous covariate depends directly on b_{i0}, violating the assumption. To isolate the issue in GM3, we consider two variations on this model: GM3A, where the random slope b_{i2} for the treatment A_{it} is removed; GM3B, where the interaction term $\beta_1 A_{it} X_{it}$ is removed. Note that the conditional independence assumption is violated in either of these variations. The details of the generative models are described below. We follow the notation of Qian et al. (2020) to allow for direct comparison, but rewrite the equations into within- and between-person models (see Raudenbush & Bryk, 2002). We accompany the equations of the GMs with graphical

representations, where random effects are represented by grey circles, observed variables by squares and relationships across variables by arrows. The path diagrams of the three data generating models shows the discrepancies between the different generative models—especially concerning the interaction effects—more clearly than DAGs.

2.1.1 Generative Model 1

In GM1, we considered a simple case with only a random intercept and a random slope for X_{it}. The outcome is generated according to the following repeated-observations or within-person model (level 1):

$$Y_{it+1} = \pi_{0i} + \pi_{1i}X_{it} + \pi_{2i}A_{it} + \pi_{3i}A_{it}X_{it} + \epsilon_{it+1}$$

with the person-level or between-person model (level 2):

$$\pi_{0i} = \alpha_0 + b_{i0}, \quad b_{i0} \sim \mathcal{N}(0, \sigma^2_{b0}),$$

$$\pi_{1i} = \alpha_1,$$

$$\pi_{2i} = \beta_0 + b_{i2}, \quad b_{i2} \sim \mathcal{N}(0, \sigma^2_{b2}),$$

$$\pi_{3i} = \beta_1.$$

By substitution, we get the single equation model:

$$
\begin{aligned}
Y_{it+1} &= \pi_{0i} + \pi_{1i} X_{it} + \pi_{2i} A_{it} + \pi_{3i} A_{it} X_{it} + \epsilon_{it+1} \\
&= (\alpha_0 + b_{i0}) + \alpha_1 X_{it} + (\beta_0 + b_{i2}) A_{it} + \beta_1 A_{it} X_{it} + \epsilon_{it+1} \\
&= \alpha_0 + \alpha_1 X_{it} + b_{i0} + A_{it}(\beta_0 + \beta_1 X_{it} + b_{i2}) + \epsilon_{it+1}.
\end{aligned}
$$

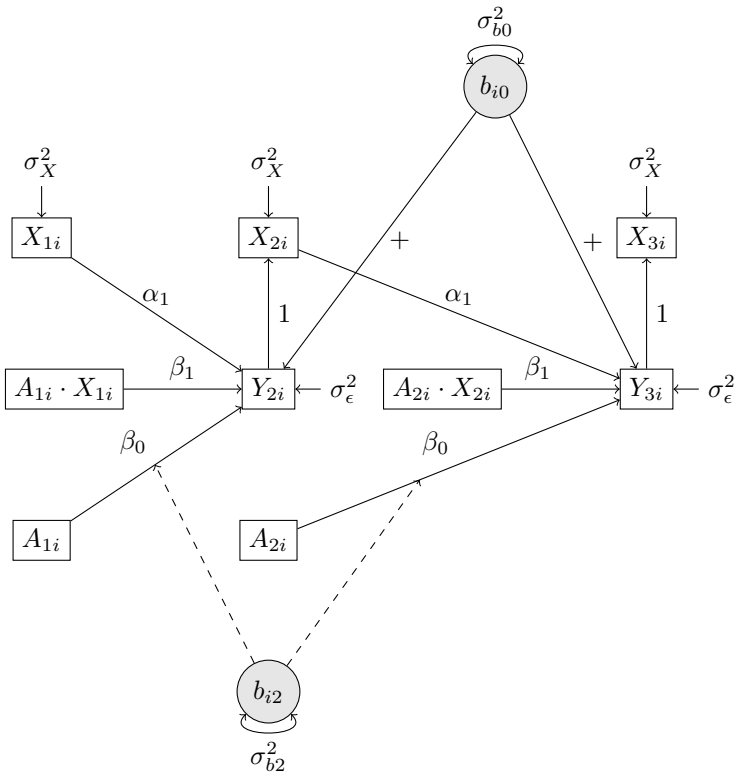
The random effects $b_{i0} \sim \mathcal{N}(0, \sigma^2_{b0})$ and $b_{i2} \sim \mathcal{N}(0, \sigma^2_{b2})$ are independent of each other. The covariate is generated as $X_{i1} \sim \mathcal{N}(0, 1)$, and for $t \geq 2$,

$$
X_{it} = Y_{it} + \mathcal{N}(0, 1).
$$

The randomization probability $p_t = P(A_{it} = 1 \mid H_{it})$ is constant at $1/2$. Thus, $A_{it} \sim$ Bernoulli(0.5) for $i = 1, \ldots, N$ and $t = 1, \ldots, T$. The exogenous noise is $\epsilon_{it+1} \sim \mathcal{N}(0, \sigma^2_\epsilon)$.

Figure 2 shows the path diagram for GM1.

Figure 2: Path diagram for Generative Model 1 ($t = 1, 2, 3$)



2.1.2 Generative Model 2

In GM2, we considered the case with a random intercept and random slopes for (1) covariate X_{it}, (2) treatment A_{it}, and (3) the interaction between A_{it} and X_{it}; and with a time-varying randomization probability for treatment. The outcome is generated according to the same repeated-observations model presented in GM1. However, the person-level model is different:

$$\pi_{0i} = \alpha_0 + b_{i0}, \quad b_{i0} \sim \mathcal{N}(0, \sigma^2_{b0}),$$

$$\pi_{1i} = \alpha_1 + b_{i1}, \quad b_{i1} \sim \mathcal{N}(0, \sigma^2_{b1}),$$

$$\pi_{2i} = \beta_0 + b_{i2}, \quad b_{i2} \sim \mathcal{N}(0, \sigma^2_{b2}),$$

$$\pi_{3i} = \beta_1 + b_{i3}, \quad b_{i3} \sim \mathcal{N}(0, \sigma^2_{b3}).$$

By substitution, we get the single equation model:

$$\begin{aligned} Y_{it+1} &= \pi_{0i} + \pi_{1i}X_{it} + \pi_{2i}A_{it} + \pi_{3i}A_{it}X_{it} + \epsilon_{it+1} \\ &= (\alpha_0 + b_{i0}) + (\alpha_1 + b_{i1})X_{it} + (\beta_0 + b_{i2})A_{it} + (\beta_1 + b_{i3})A_{it}X_{it} + \epsilon_{it+1} \\ &= \alpha_0 + \alpha_1 X_{it} + b_{i0} + b_{i1}X_{it} + A_{it}\left(\beta_0 + \beta_1 X_{it} + b_{i2} + b_{i3}X_{it}\right) + \epsilon_{it+1}. \end{aligned}$$

The random effects $b_{ij} \sim \mathcal{N}(0, \sigma^2_{bj})$, for $j = 0, 1, 2, 3$, are independent of each other. The covariate is generated as $X_{i1} \sim \mathcal{N}(0, 1)$, and for $t \geq 2$,

$$X_{it} = Y_{it} + \mathcal{N}(0, 1).$$

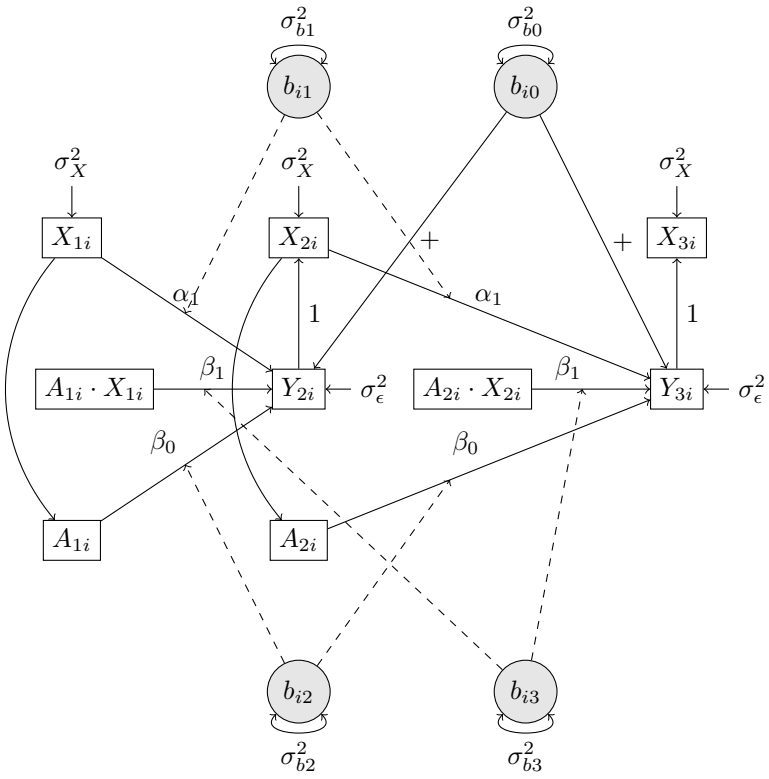
The randomization probability depends on X_{it}:

$$p_t = P(A_{it} = 1 \mid H_{it}) = \begin{cases} 0.7 & \text{if } X_{it} > -1.27, \\ 0.3 & \text{if } X_{it} \leq -1.27, \end{cases}$$

where the cutoff -1.27 was chosen so that p_t equals 0.7 or 0.3 for about half of the time. In other words, if the value of the covariate for any given person and time point is above the cutoff, the probability of receiving the treatment p_t is 0.7; otherwise, it is 0.3. Accordingly, $A_{it} \sim \text{Bernoulli}(p_t)$ for $i = 1, \ldots, N$ and $t = 1, \ldots, T$. The exogenous noise is $\epsilon_{it+1} \sim \mathcal{N}(0, \sigma^2_\epsilon)$.

Figure 3 shows the path diagram for GM2.

Figure 3: Path diagram for Generative Model 2 ($t = 1, 2, 3$)



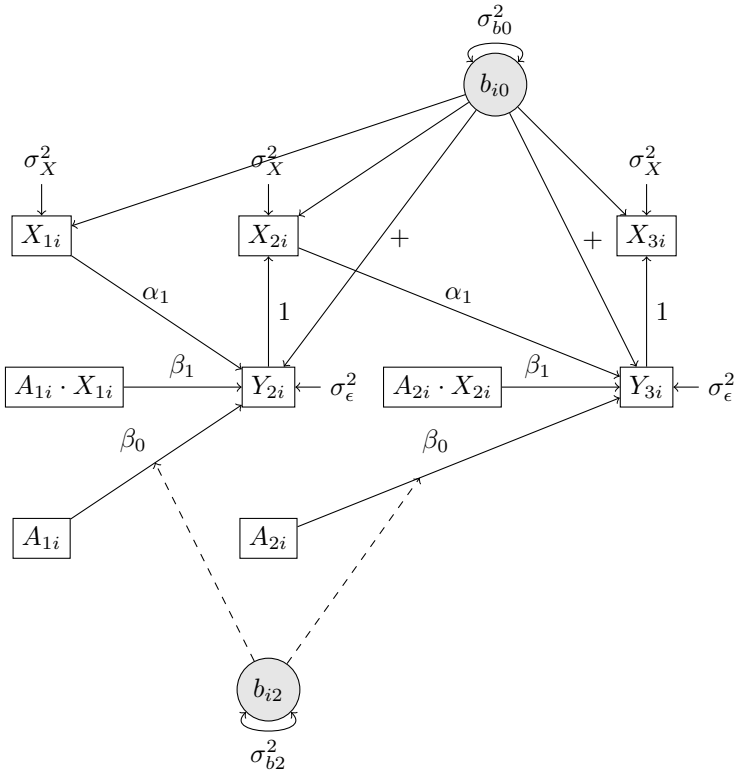
2.1.3 Generative Model 3

GM3 is the same as GM1, except that the covariate X_{it} depends directly on b_{i0}:

$$X_{i1} \sim \mathcal{N}(b_{i0}, 1), \quad X_{it} = Y_{it} + \mathcal{N}(b_{i0}, 1) \text{ for } t \geq 2.$$

Figure 4 shows the path diagram for GM3.

Figure 4: Path diagram for Generative Model 3 ($t = 1, 2, 3$)

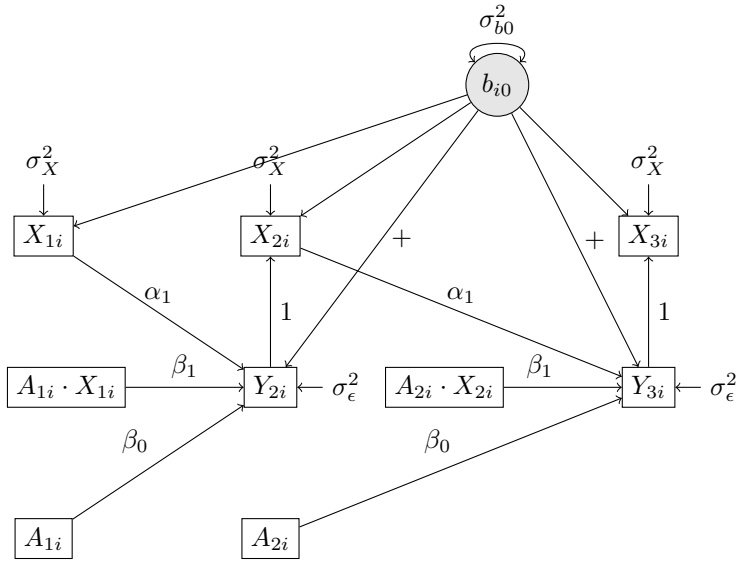


2.1.4 Generative Model 3A

GM3A is the same as GM3, except that the random slope b_{i2} for the treatment A_{it} is removed. The single equation model then becomes:

$$Y_{it+1} = \alpha_0 + \alpha_1 X_{it} + b_{i0} + A_{it}(\beta_0 + \beta_1 X_{it}) + \epsilon_{it+1}.$$

Figure 5: Path diagram for Generative Model 3A ($t = 1, 2, 3$)

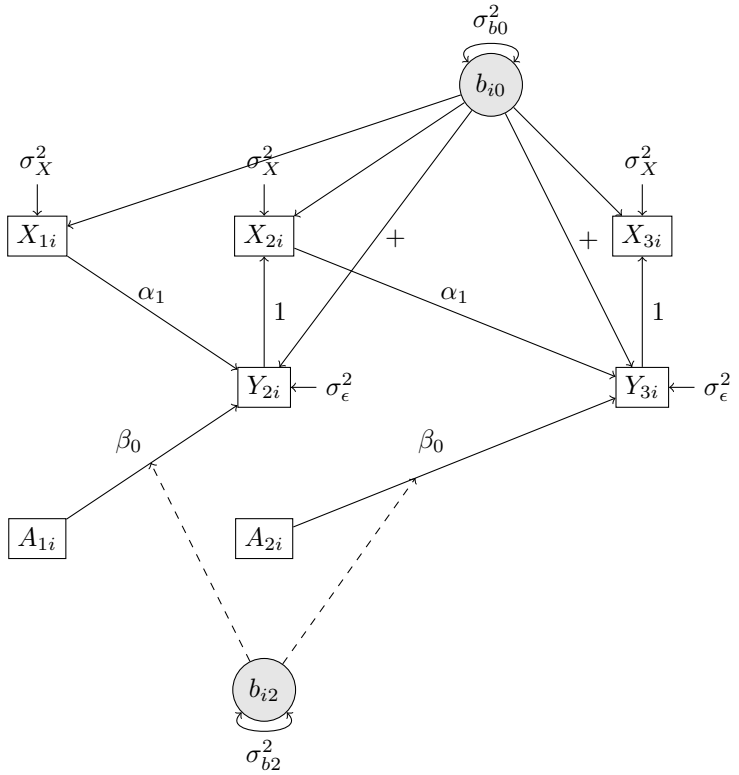


2.1.5 Generative Model 3B

GM3B is the same as GM3, except that the interaction term $\beta_1 A_{it} X_{it}$ is removed. The single equation model then becomes:

$$Y_{it+1} = \alpha_0 + \alpha_1 X_{it} + b_{i0} + A_{it}(\beta_0 + b_{i2}) + \epsilon_{it+1}.$$

Figure 6: Path diagram for Generative Model 3B ($t = 1, 2, 3$)



2.1.6 Parameter Values

The following parameter values were adapted from Qian et al. (2020):

$$\alpha_0 = -2, \quad \alpha_1 = -0.3, \quad \beta_0 = 1, \quad \beta_1 = 0.3,$$

$$\sigma^2_{b0} = 4, \quad \sigma^2_{b1} = \frac{1}{4}, \quad \sigma^2_{b2} = 1, \quad \sigma^2_{b3} = \frac{1}{4}, \quad \sigma^2_\epsilon = 1.$$

2.2 Path Diagrams and Conditional Independence

Qian et al. (2020) proposes the use of the conditional independence assumption to identify whether bias may occur, which is given by:

$$X_{it} \perp (b_{i0}, b_{i1}) \mid H_{it-1}, A_{it-1}, Y_{it}.$$

where H_{it-1} refers to the history of the set of covariates, which in this case are all observations of covariate X_{it} prior to the current timepoint t. This allows X_{it} to be endogenous, but the endogenous covariate X_{it} can only depend on the random effects through variables observed prior to X_{it}. If the only endogenous covariates are functions of prior treatments and prior outcomes, then the assumption automatically holds.

When inspecting Figure 2 and Figure 3, we may notice that X_{it} becomes independent of the random effects after conditioning on Y_{it}. On the other hand, we can see that this assumption is violated in GM3/3A/3B, as X_{it} depends directly on b_{i0} and can thus not be made independent of the random effects by conditioning on prior variables such as Y_{it} (see Figure 4, Figure 5 and Figure 6). Thus, we would expect biased estimates of the treatment effect for GM3/3A/3B.

2.3 Backdoor Criterion and DAGs

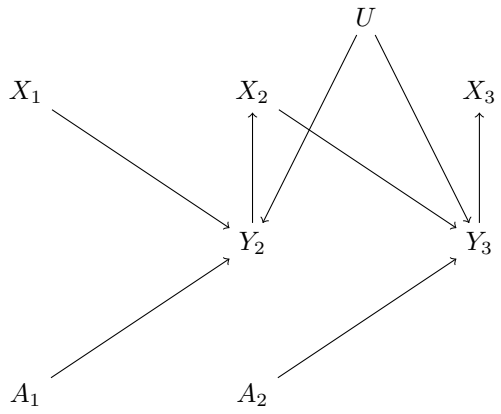
DAGs are a useful tool for representing causal relationships between variables and to evaluate the assumptions needed for causal identification. According to the backdoor criterion (Pearl, 1988, 2009), a requirement for causal identification, causal effects can be identified by blocking non-causal paths through conditioning on intermediate variables (e.g., controlling or matching). If any non-causal paths cannot be blocked due to omitted variables or measurement error, treatment and outcome remain linked via backdoor paths, leading to biased estimates of the treatment effect (Kim & Steiner, 2021).

We formulated the DAGs in `dagitty`, where the random disturbance b_{0i} was represented by the node U (e.g., Kim & Steiner, 2021). The DAGs for the first three observa-

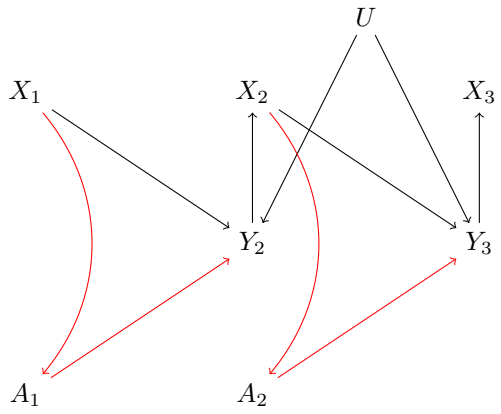
tions of the three data generating models are presented in Figure 7.

Figure 7: DAGs for Generative Models 1, 2, 3, 3A, 3B (t = 1, 2, 3)

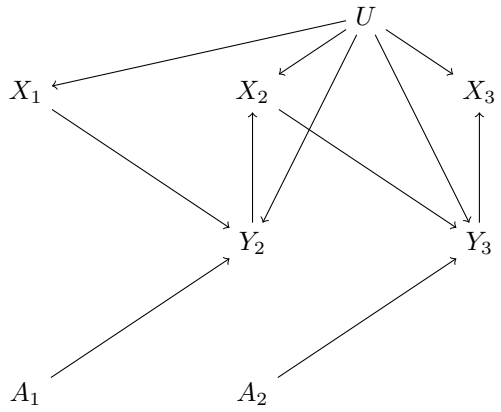
(a) GM 1



(b) GM 2



(c) GM 3, 3A, 3B



Note. The red arrows show the biased back-door path(s) in the treatment efffect (before controlling for X_{it}).

When applying Pearl's backdoor criterion to GM1/3/3A/3B, it may be observed that there exists no backdoor path in the treatment effect $A_{it} \rightarrow Y_{it+1}$, as A_{it} does not have any parents. While we need not control for covariate X_{it} to obtain an unbiased total effect, doing so should not introduce bias.

On the other hand, in GM2, there is a backdoor path in the treatment effect: $A_{it} \leftarrow X_{it} \rightarrow Y_{it+1}$ (see Figure 7b). More specifically, X_{it} is a confounder in the relationship between A_{it} and Y_{it+1}. However, controlling for X_{it} blocks this backdoor path, making the treatment effect unbiased. In other words, the history of covariate X_{it} is a sufficient adjustment set for the treatment effect.

All things considered, according to the backdoor criterion, controlling for the covariate X_{it} should not result in biased estimates of the treatment effect for any of the generative models.

2.4 Data Analysis

We evaluated the performance of the models across a total of 30 different settings, each replicated 1,000 times, by systematically varying the following factors:

- **Generative Models (GM):** 1, 2, 3, 3A, 3B
- **Number of timepoints (T):** 10, 30
- **Sample size (N):** 30, 100, 200

All data generation and estimation was performed in `R`, version 4.4.2 (Team, 2024). After the generation of data generation for any given setting, several models were fit. To fit the standard MLM, the `lmer` function from the R-package `lme4` (Bates et al., 2015) was employed with restricted maximum likelihood estimation. For the MLM, the analytical models were equivalent to each of the respective data-generating models. To fit the GEE with the "exchangeable", "independent" and "AR(1)" working correlation structures, the `geeglm` function from the R-package `geepack` (Halekoh et al., 2006) was employed with the identity link function. Since the random effects are not explicitly modelled in GEE, the analytical GEE models simply contain only the fixed effects of the generative model at hand.

3 Results

Table 1 presents the simulation results for each of the generative and analytical models. The estimates for the analytical MLM may be interpreted in terms of bias. Here we find that there is little to no bias for GM1/2/3A/3B and substantial bias for GM3. Thus, once we remove either the dependency of the random intercept with the covariate (GM1), the random slope b_{i2} (GM3A) or the interaction β_1 (GM3B) from GM3, the bias dissapears or becomes extremely small. The bias in GM3 decreases as the number of timepoints T increases from 10 to 30. Note that the MLM model fitting success rates are particularly poor for GM2, where in the worst case, only 87 of the 1000 models were fitted.

For the GEE with independence, the values refer to the difference between the estimated marginal effect—which should be unbiased under endogenous covariates (see Pepe & Anderson, 1994)—and the specified conditional effect. Here we find that there is a enormous difference between these effects for GM2, which increases along with an increase in T and N, up to a difference of more than 6,000. This is followed by a difference of around .07-.09 for GM1, .02-.04 for GM3, ≤ 0.015 for GM3B and close to zero for GM3A. The GEE models fitted succesfully for all settings.

4 Discussion

This report employed both graphical methods and data simulations to understand and explain the issue of endogenous covariates. Now we will discuss the findings relating to the two research questions, while excluding GM2 due to model fitting issues.

Using the conditional independence assumption of Qian et al. (2020), we would expect, based on the path diagrams, that the treatment effect would be biased for GM3, 3A

Table 1: Simulation results for Generative Models 1, 2, 3, 3A and 3B over 1000 replications

			MLM			GEE-IND		
GM	T	N	Bias	SD	SR	Difference	SD	SR
1	10	30	0.000	0.238	0.998	0.071	0.296	1
		100	-0.012	0.129	1.000	0.074	0.169	1
		200	0.003	0.093	0.999	0.085	0.116	1
	30	30	-0.001	0.203	0.998	0.085	0.224	1
		100	-0.007	0.107	0.996	0.083	0.123	1
		200	0.001	0.079	0.996	0.094	0.088	1
2	10	30	0.011	0.282	0.925	0.306	1.630	1
		100	0.005	0.147	0.881	0.565	1.836	1
		200	0.008	0.103	0.844	0.935	1.887	1
	30	30	0.000	0.220	0.603	182.565	4751.387	1
		100	-0.014	0.114	0.247	-356.412	39799.388	1
		200	-0.013	0.087	0.087	6319.792	136201.790	1
3	10	30	-0.052	0.245	0.999	0.020	0.249	1
		100	-0.064	0.134	1.000	0.024	0.141	1
		200	-0.051	0.096	1.000	0.035	0.097	1
	30	30	-0.024	0.206	0.997	0.030	0.208	1
		100	-0.030	0.108	0.996	0.027	0.112	1
		200	-0.023	0.080	0.997	0.037	0.081	1
3A	10	30	0.000	0.126	1.000	-0.004	0.157	1
		100	0.004	0.073	1.000	0.001	0.090	1
		200	0.002	0.048	1.000	-0.001	0.062	1
	30	30	-0.001	0.071	1.000	-0.003	0.090	1
		100	0.000	0.040	1.000	-0.001	0.051	1
		200	0.000	0.028	1.000	0.000	0.036	1
3B	10	30	0.001	0.217	0.999	-0.013	0.241	1
		100	-0.008	0.121	1.000	-0.008	0.138	1
		200	0.005	0.087	1.000	0.003	0.097	1
	30	30	0.000	0.193	1.000	-0.004	0.200	1
		100	-0.008	0.103	0.997	-0.007	0.108	1
		200	0.001	0.075	0.999	0.001	0.080	1

Note. SR: model fitting success rate. Bias: $\hat{\beta}_{0,MLM} - \beta_{0,MLM}$. Difference: $\hat{\beta}_{0,GEE} - \beta_{0,MLM}$. SD: standard deviation of estimates across replications.

and 3B. On the other hand, the backdoor criterion suggested the absence of bias for all generative models. While Qian et al. (2020) show that GM3 is the only model with bias in the treatment effect, the backdoor criterion failed to identify this bias, as there is no backdoor path in the treatment effect. This may be explained by the fact that the DAG does not impose restrictions based on (a) the random slopes and (b) interaction effects. Concerns regarding the use of Pearl's backdoor criterion in situations with interaction effects have been voiced by several people (see Weinberg (2007); Attia et al. (2022)).

The first research question—pertaining to the extent of treatment effect bias in MLM estimates of generative model that were nested in GM3—was investigated using the analytical multilevel model. First, we reproduced the findings by Qian et al. (2020) that the estimators are consistent for GM1 and GM2, but inconsistent for GM3. Using additional generative models, we found that bias became indiscernable when removing from GM3 either the dependency between the random intercept and covariate (GM1), the random slope for treatment (GM3A) or the interaction effect (GM3B). This finding is in sharp contrast to the suggestion of the conditional independence assumption that the treatment effect would be biased for GM3, 3A and 3B.

The second research question—related to the discrepancy between marginal and conditional interpretations of the treatment effect—was assessed with analytical GEE with working independence. Here we found extreme differences between the estimated marginal and specified conditional effect for GM2, suggesting that the marginal interpretation breaks down the most for this generative model[1]. Hence, for this GM, a false interpretation of the MLM parameters as marginal, would potentially have great inferential consequences. For GM1 and GM3, there smaller but still noticeable differences between

[1]Note, however, that this generative model may not be plausible given the extreme spread across the covariate and treatment variables.

the marginal and conditional effect. This suggests that the marginal interpretation of the treatment effect may be recovered for GM3, 3A and 3B, but not for GM2. Especially for GM3A, this difference was practically indescernable, suggesting that the marginal interpretation of the treatment effect may be recovered. Conversely, Qian et al. (2020) notes that if the random effect in the model does not interact with the treatment variable, the interaction recovers its marginal interpretation but the treatment effect does not (p. 382). This difference in conclusions may be explained through the difference in approach: while Qian et al. (2020) provides an analytical answer, the current study provides approximations through simulations.

For the GM2 setting of Qian et al. (2020), we found several issues, which were most pronounced for $T = 30$. First, we noticed extreme model fitting issues for the MLM, due to, among other things, a lack of convergence and singularity. It should be noted that unlike the script used here, Qian et al. (2020) deals only with errors of the `lmer()` function, but not with warnings (e.g., pertaining to non-convergence) in their script. This discrepancy may explain the slightly different estimates of MLM bias for GM2. Second, we found extremely large GEE estimates of the treatment effect. This may be explained by the fact that the values of the covariate and outcome were also extremely great, often exceeding a million. All things considered, this suggests that GM2 may be a poorly specified model.

5 References

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