Appendix B. Sensitivity Analyses

2 Appendix B: Sensitivity analyses

We varied a number of features of our model to check bias as a result of the outcome dependent visit process. We focused on the all irregular case since that is where there is the most bias and simulated sample sizes per cluster of either 6.4 or 12.8. We used 1000 clusters. We used three fitting methods for all scenarios: maximum likelihood mixed models, GEE independence, and GEE exchangeable (except for GEE exchangeable for the Poisson outcome data which would not converge). The details of the settings are given below.

Except for the outcome distribution sensitivity analysis, all the models were linear mixed models. We considered two forms of outcome dependence: dependence on the conditional linear predictor and dependence on a lagged value of the outcome. We simulated no outcome dependence (as a check) and moderate outcome dependence. Our base outcome model was a standard linear mixed model with normally distributed random intercepts and slopes with time and fixed effects of a group variable, the time variable and the group by time interaction. 1000 replications were conducted for each simulation scenario.

The features evaluated for the sensitivity analyses were differing:

1. Degree of non-normal errors using a hidden Markov model to generate 10% of the data from an outlying distribution,
2. Degree of autocorrelated errors,
3. Distributions of the random effects: heavy tailed and skewed,
4. Correlations among the random effects,
5. Random effects variances, and
6. Outcome distributions.

The base outcome model used was a linear mixed model with random slopes and intercepts, variance 1, correlation 0.5 as given in (2). The errors were assumed to be independent with variance 1. The fixed effect coefficients

were set to $\beta_0 = 0, \beta_t = -0.5, \beta_g = 0.5,$ and $\beta_i = 1.5$ and there were 1,000 clusters. The outcome dependent visit models were those given by (6) and (7) of the main report. To generate the non-normal random effects distributions used in the main report we used independent Tukey distributions, Y_i, and generated the random effects via $b_0 = \sqrt{1-\rho} * std(Y_0) + \sqrt{\rho} * std(Y_2)$ and $b_1 = \sqrt{1-\rho} * std(Y_1) + \sqrt{\rho} * std(Y_2)$, where $std(\cdot)$ represents the value standardized to mean 0 and standard deviation 1. Tukey(g=0.0001, h=0.2) was used for the heavy tailed distribution and Tukey(g=0.446, h=0.050) was used for the skewed.

The variations considered here are autocorrelated errors with autocorrelation of 0, 0.5, 0.9 and 0.99 and error terms generated according to a two-state Hidden Markov process. We also considered other settings for values of the random effects variance-covariance matrix and binary and Poisson distributed outcomes. To generate the two-state error terms we simulate from normal distributions with mean -δ with probability 0.9 and δ with probability 0.1. That is then standardized to mean 0 and variance 1. We also made the errors autocorrelated to mimic data such as the example given in the main report. The mean residence time in the first state was set to 5.25 time steps. The end result is an autocorrelated, bimodal (for large enough δ) error distribution.

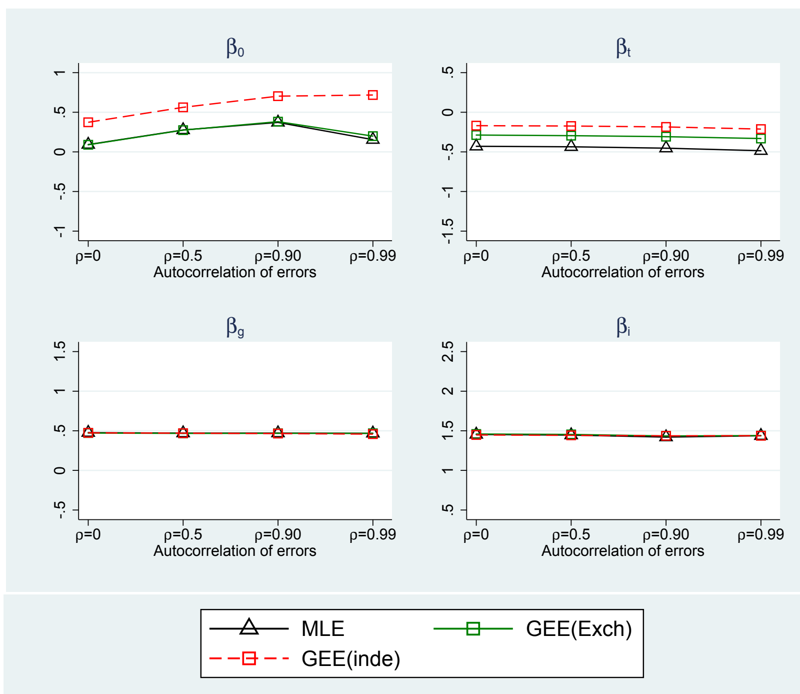
For the non-normal outcome distributions we modified the parameter settings slightly. For the Poisson we used $\text{var}(b_0) = 1$, $\text{var}(b_1) = 0.5$ (so a SD of 0.71), correlation 0.5. So only $\text{var}(b_1)$ is changed compared to base case. The fixed effect coefficients were set to $\beta_0 = -0.5, \beta_t = -0.5, \beta_g = 0.5$, and $\beta_i = 1.5$. So only β_0 is changed compared to base case. For the logistic we used the same parameters as for the Poisson except that $\beta_0 = -1.5$.

For each scenario above there are two types of outcome dependent visits, two degrees of outcome dependence and two sample sizes, so 8 variations. There was not any bias observed under the no outcome dependence situation for any of the estimators so we do not discuss those further. There was no appreciable difference in the results for the target sample sizes of 6.4 and 12.8, so we focus discussion on the sample size of 6.4. Except for the hidden Markov sensitivity analysis, the bias was similar for the two outcome dependence processes. So for most of the sensitivity checks it suffices to look at one of the outcome dependent visit processes. If there were minor differences we present the one with larger bias. In each of the sections below we display a plot of the bias versus the sensitivity factor (e.g., degree of autocorrelation) along with a brief summary.

2.1 Autocorrelated error terms

As displayed in Figure 1, no bias was observed in the group or interaction effects. As we have seen in other simulations, GEE(inde) is more severely biased than the other two. Moderate autocorrelation leads to bias for ML and GEE(exch) in the intercept.

Figure 1: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function of the autocorrelation in the errors. Simulated under a lag Y informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0.654Y_{i,j-5}$, and linear mixed outcome model with random intercepts and slopes.



2.2 Bimodal and autocorrelated error terms

In this section we investigate the influence of non-normal errors using a hidden Markov model to generate 10% of the data from an outlying distribution. As displayed in Figures 2 and 3, the outcome dependent visit processes give slightly different results so we present both. There is no bias in the group or interaction effects for either outcome dependent visit process. As we have seen before, GEE(inde) is more severely biased than the other two. A large degree of outlying errors leads to bias in the intercept for ML and GEE(exch).

2.3 Different random effects variances

As displayed in Figure 4, no bias was observed in the group or interaction effects. As before, GEE(inde) is more severely biased than the other two. Increasing variance leads to a bit more bias in the time effect for both the GEE methods.

2.4 Different outcome distributions

Because the GEE fits are marginal models we present both the $\gamma_Y = 0$ and $\gamma_Y = 0.654$ results for the lagged Y dependence. Assessment of bias requires a comparison of the two plots. For the normal and binomial outcomes the results are as predicted by the theory: there is a modest bias in the intercept and time effect (as judged by the slightly larger values in Figure 6 compared

Figure 2: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function of the bimodality of the error distribution. Simulated under a lag Y informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0.654 Y_{i,j-5}$, and linear mixed outcome model with random intercepts and slopes.

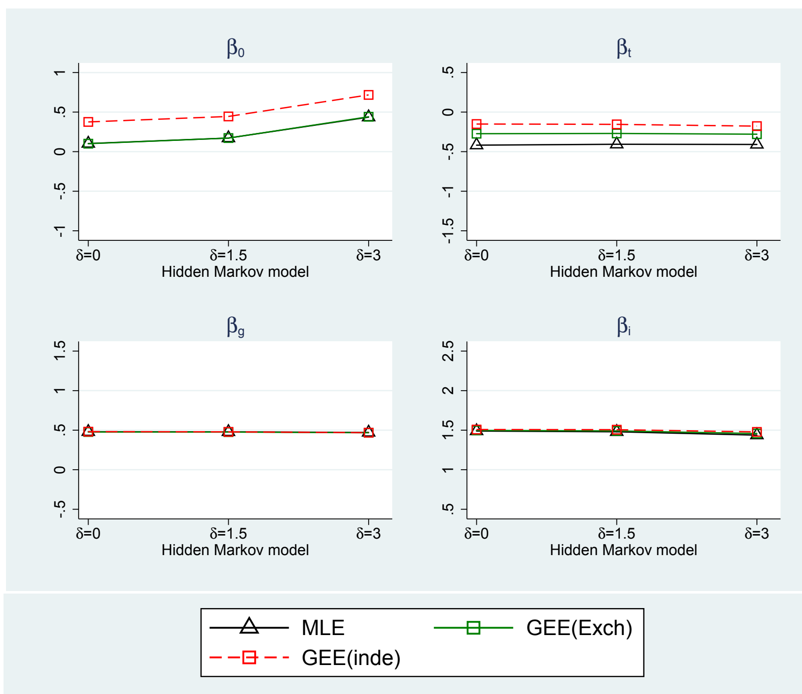


Figure 3: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function of the bimodality of the error distribution. Simulated under a conditional mean informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0.654\text{E}[Y \mid b]$, and linear mixed outcome model with random intercepts and slopes.

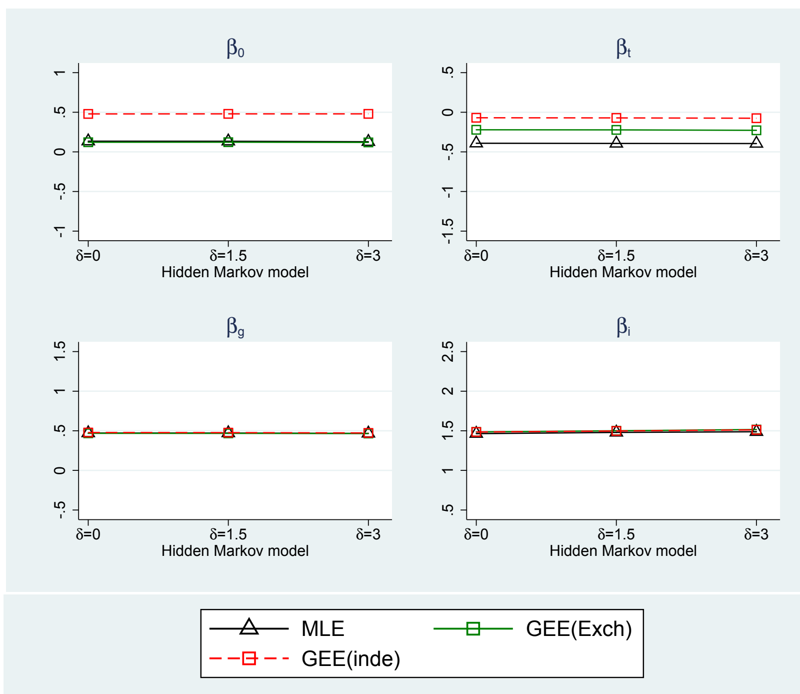
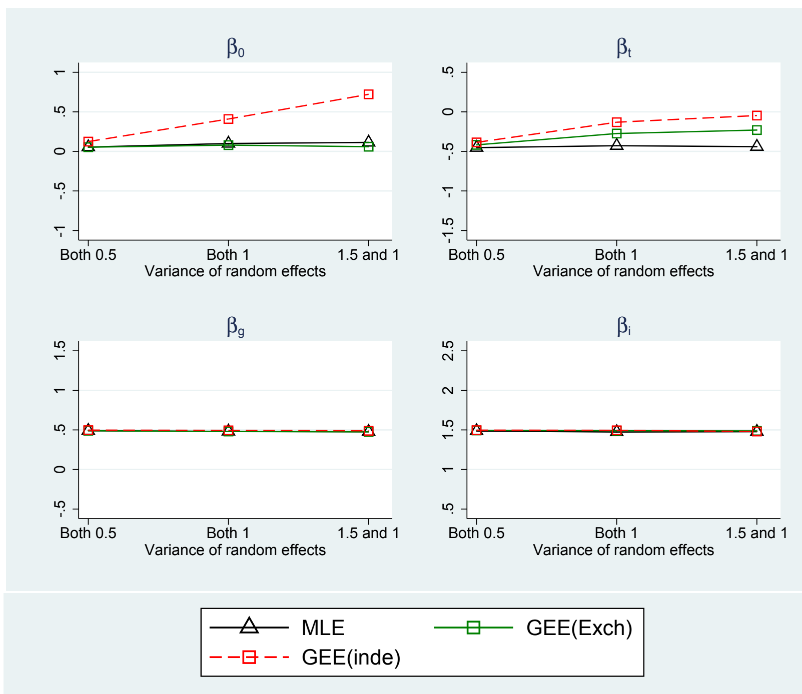


Figure 4: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function of the random effects variance. Simulated under a lag Y informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0.654Y_{i,j-5}$, and linear mixed outcome model with random intercepts and slopes.



to Figure 5) but not in the time or interaction effects as predicted by theory.

However, the situation with the Poisson distribution is quite different. First, the GEE-exchangeable fits were not possible because of non-convergence of the algorithms in estimating the exchangeable correlation structure (verified in SAS as well as Stata). Second, the GEE-independence fit demonstrated bias in all the parameter estimates as gauged by the differences between Figures 6 and 5 (height of red square for the Poisson distribution). So for Poisson distributions, GEE fits are clearly biased, whereas this simulation (albeit limited) did not exhibit significant bias for the MLE.

Figure 5: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function the outcome distribution. Simulated under a non-informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0Y_{i,j-5}$, and generalized linear mixed outcome model with random intercepts and slopes.

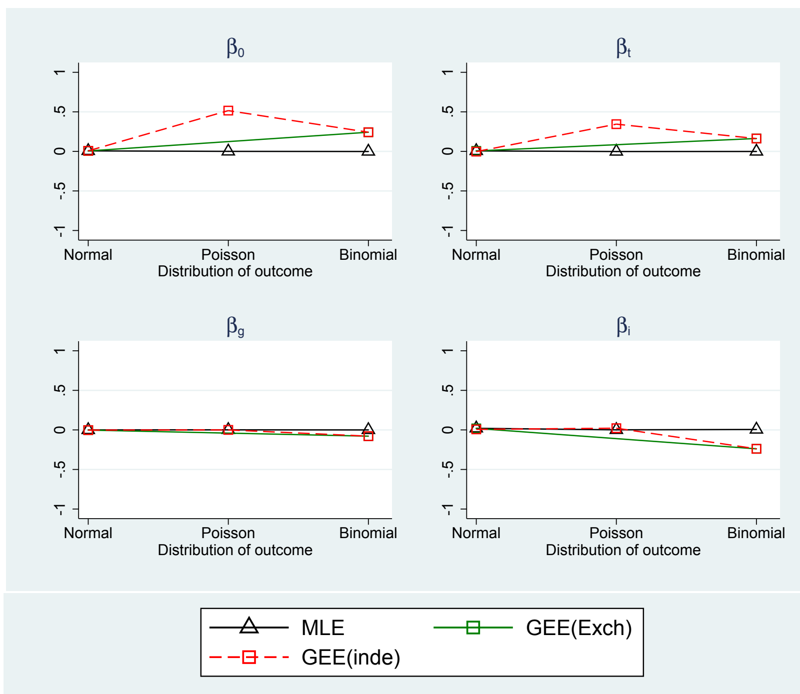


Figure 6: Simulated mean values of the maximum likelihood (MLE), GEE-exchangeable and GEE-independence regression coefficient estimators as a function the outcome distribution. Simulated under a lag Y informative visit process with a logit link, i.e., $\text{logit}(P(R_{it} = 1)) = -5 + 0.654Y_{i,j-5}$, and generalized linear mixed outcome model with random intercepts and slopes.