

Quantifying PQL bias in estimating cluster-level covariate effects in generalized linear mixed models for group-randomized trials

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Abstract

We derive the asymptotic bias and variance of the penalized quasiliikelihood (PQL) estimator of the cluster-level covariate effect in generalized linear mixed models for group-randomized trials where the number of clusters n is small and the cluster size m is large. We show that the leading asymptotic bias is of order $O_p(m^{-1})$ and the leading asymptotic variance is of order $O_p(n^{-1})$. The practical implication of our results is that the PQL method works well in settings involving small numbers of large clusters which are typically in grouped randomized trials. We illustrate the results using simulation studies.

Some key words: Asymptotic bias; Asymptotic variance; Generalized linear mixed models; Penalized quasiliikelihood.

1 INTRODUCTION

Group-randomized trials are becoming increasingly popular as a tool for evaluating the efficacy of behavioral health interventions, particularly those involving providers such as group therapists or primary care physicians as well as other natural groupings like schools or neighborhood community centers. These trials are distinguished by randomizing intact units/groups of individuals (e.g., therapy groups, primary care practices, classrooms or neighborhoods) to various conditions (e.g., cognitive behavior therapy, depression specialist, method of teaching, or community-level classes).

These trials are also known as cluster-randomized trials in other literature (see, for example, Donner and Klar, 2000). Group-randomized trials are further distinguished by having a small number of clusters with a large number of observational units within each cluster. The goal of a typical behavioral intervention study is to compare the rates of various adverse health outcomes or risky lifestyle behaviors between intervention arms. The general goal is to make cluster-level inference of the efficacy of the intervention. These types of studies are often interested in modeling outcomes (e.g., number of risky 'events' in the past month, disease status yes/no, etc.) as a function of confounding and/or mediating variables while adjusting for the potential correlation of responses from observations within the same cluster. From an analytic perspective, there are several challenges to appropriately modeling such data since it is important to account for the clustered nature of the responses, especially in settings when there are a few large clusters/groups where the standard asymptotic results are questionable.

Two popular approaches for modeling clustered data are via population-averaged (PA) models fitted by generalized estimating equations (GEEs) and subject-specific models fitted using generalized linear mixed models (GLMMs). The GEE approach is attractive in that it provides unbiased estimates while properly adjusting for possible misspecification of the correlation of responses from the same cluster, but these properties may be doubtful in settings involving small numbers of large clusters (see, for example, Bellamy et al, 2000; Mancl and Leroux, 1996). Generalized linear mixed models account for the within-cluster correlation by directly introducing random effects in model specification. Inference in GLMMs is challenged by the required numerical integration in the likelihood function. In addition to numerical quadrature and Markov Chain Monte Carlo techniques for integration, the penalized quasiliikelihood (PQL) approach (Breslow and Clayton, 1993; Green, 1987) provides an alternative easy approach to estimating covariate effects in GLMMs. However, various authors have noted that covariate effects based on the PQL may be asymptotically biased (see, for example, Neuhaus and Segal, 1997; Breslow and Lin, 1995; Lin and Breslow, 1996). Breslow and Lin (1995) and Lin and Breslow (1996) derived asymptotic bias expressions for PQL regression coefficient and variance component estimators in settings where there are a large number of small clusters. Their results are not applicable to group-randomized trial settings where there are a small number of large clusters.

There have been related asymptotic explorations of the PQL estimators in the context of small area estimation. Jiang and Lahiri (2001) considered the asymptotic properties of estimating random effects in settings where the number of independent observations within clusters gets large, but here we are interested in the asymptotic bias associated with estimating fixed-effects. Jiang (1999) examined the asymptotic behavior of PQL-type estimators when both the numbers of clusters and observations within clusters increase. This result is not directly applicable to group-randomized trial settings where there is often a small number of clusters.

In previous work, we explored the bias associated with PQL methods in group-randomized trial settings via simulation studies and observed good empirical results in estimating covariate effects, especially for large cluster sizes (Bellamy et al, 2000). Ten Have and Localio (1999) reported simulation results showing that PQL performed well with small numbers of large clusters, whereas numerical integration did poorly in settings where there are few clusters. Vonesh et al (2002) investigated the asymptotic distribution of the PQL estimator when the number of both the number of clusters and the cluster size go to infinity and showed the PQL estimator performed well in such settings.

In this paper we explore more rigorously those empirical findings by deriving expressions for the asymptotic bias and variance associated with estimating cluster-level covariate effects in a GLMM using the PQL approach in settings which have a small number of large clusters such as group-randomized trials. The paper is organized as follows. We first present in Section 2 the GLMM and the PQL method. We derive in Section 3 an expression for the asymptotic bias in estimating the cluster-level covariate effects via the PQL and the asymptotic variance of the PQL estimator. We consider in Section 4 the forms of the bias and variance expressions for common special cases. We present in Section 5 the results from a simulation study and close with a discussion in Section 6.

2 THE GENERALIZED LINEAR MIXED MODEL

2.1 MODEL FORMULATION

Consider data from a study involving n clusters. For simplicity of presentation, we assume there are an equal number of m observations per cluster. Generalization of our results to unequal cluster

size settings are straightforward and are presented at the end of Section 3. In grouped-randomized trials, n is often small and m is often large. For the j th observation ($j = 1, \dots, m$) in cluster i ($i = 1, \dots, n$), we observe a response y_{ij} , and a $p \times 1$ vector of cluster-specific covariates \mathbf{x}_i . Generalized linear mixed models (GLMMs) provide a broad class of random effects models to model such clustered data. Conditional on the cluster-specific unobserved random effects b_i , the outcomes y_{ij} are assumed to be independent and follow the exponential family

$$\ell_i(\boldsymbol{\beta}; b_i) = \sum_{j=1}^m \frac{a_{ij}}{\phi} \{y_{ij}\eta_{ij} - c(\eta_{ij})\} + k(y_{ij}, \phi), \quad (1)$$

where η_{ij} is a canonical parameter, a_{ij} is a known weight, ϕ is a scale parameter, and $c(\cdot)$ and $k(\cdot)$ are some known functions. The conditional mean of y_{ij} is $\mu_{ij} = E(y_{ij}|b_i) = c'(\eta_{ij})$ and is related to the covariate vector \mathbf{x}_i and the random effect b_i through a generalized linear model (Breslow and Lin, 1995)

$$g(\mu_{ij}) = \mathbf{x}_i\boldsymbol{\beta} + b_i, \quad (2)$$

where $g(\cdot)$ is a monotone link function and $b_i \sim N(0, \theta)$. We restrict in this paper to canonical link functions which satisfy $g(\mu_{ij}) = \eta_{ij}$, $\text{var}(y_{ij}|b_i) = \phi a_{ij}^{-1} v(\mu_{ij})$ and $g'(\mu_{ij}) = 1/v(\mu_{ij})$ (McCullagh and Nelder, 1989). The observed data likelihood is hence

$$L(\boldsymbol{\beta}, \theta) = \prod_{i=1}^n \frac{1}{\sqrt{2\pi\theta}} \int \exp \{ \ell_i(\boldsymbol{\beta}; b_i) - b_i^2/2\theta \} db_i. \quad (3)$$

2.2 PQL ESTIMATION OF GLMM

Because the integrated likelihood (3) does not usually have a closed form expression, Breslow and Clayton (1993) proposed estimation of the regression coefficients $\boldsymbol{\beta}$ using the penalized quasi-likelihood (PQL) method by applying the Laplace approximation to the integrated loglikelihood function. The PQL likelihood can be written as (Breslow and Lin, 1995),

$$\ell_p(\boldsymbol{\beta}, \theta) = \sum_{i=1}^n \left(\tilde{\ell}_i - \frac{\tilde{b}_i^2}{2\theta} \right), \quad (4)$$

where \tilde{b}_i satisfies $\tilde{b}_i = \theta \partial \ell_i(\boldsymbol{\beta}, b_i) / \partial b_i|_{b_i=\tilde{b}_i}$ and

$$\tilde{\ell}_i = \ell_i(\boldsymbol{\beta}, \tilde{b}_i) = \sum_{j=1}^m \frac{a_{ij}}{\phi} \{y_{ij} \tilde{\eta}_{ij} - c(\tilde{\eta}_{ij})\} + k(y_{ij}, \phi),$$

where $\tilde{\eta}_{ij} = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \tilde{b}_i$.

In this paper, we assume θ is known and study the asymptotic bias and variance of the PQL estimator of the regression coefficients $\hat{\boldsymbol{\beta}}$ in grouped randomized trial settings where the number of clusters n is small and fixed and the cluster size m is large and goes to infinity. We will derive the asymptotic bias for the general GLMM (2) and then consider various special cases, including a random effects logistic regression model.

3 ASYMPTOTIC BIAS AND VARIANCE OF ESTIMATED CLUSTER-LEVEL PQL COVARIATE EFFECTS

The PQL estimator of $\boldsymbol{\beta}$ is the solution of the estimating equation obtained from maximizing (4) with respect to $\boldsymbol{\beta}$ and simultaneously computing \tilde{b}_i ($i = 1, \dots, n$) as follows

$$\sum_{i=1}^n \sum_{j=1}^m \mathbf{x}_i \frac{a_{ij}}{\phi} \{y_{ij} - \mu(\mathbf{x}_i^T \hat{\boldsymbol{\beta}} + \tilde{b}_i)\} = 0, \quad (5)$$

and

$$\sum_{j=1}^m \frac{a_{ij}}{\phi} \{y_{ij} - \mu(\mathbf{x}_i^T \hat{\boldsymbol{\beta}} + \tilde{b}_i)\} = \frac{\tilde{b}_i}{\theta}, \quad (i = 1, \dots, n), \quad (6)$$

where $\mu(\cdot) = g^{-1}(\cdot)$.

Our goal is to derive the asymptotic bias of the PQL estimator when n is small and m goes to infinity. We proceed this by deriving an asymptotic expansion of the PQL estimator $\hat{\boldsymbol{\beta}}$, the solution to the estimating equations in (5) and (6), about its true value $\boldsymbol{\beta}$ for fixed n and large m . Since the second component of the estimating equations (6) involves solving n cluster-specific equations, standard M -estimation theory does not apply (see, for example, Van der vaart 1998 or Akritas 1991).

We first pre-multiply each of the n components of (6) by \mathbf{x}_i then sum over the index i and apply equation (5). This gives the constraint

$$\sum_{i=1}^n \mathbf{x}_i \tilde{b}_i = 0, \quad (7)$$

where \tilde{b}_i is the value of b_i that satisfies both (5) and (6), simultaneously.

Equation (6) can be written as

$$\bar{y}_{i.} - \mu(\mathbf{x}_i^T \hat{\boldsymbol{\beta}} + \tilde{b}_i) = \frac{\tilde{b}_i \phi}{m \bar{a}_{i.} \theta}, \quad (8)$$

where $\bar{y}_{i.} = \sum_{j=1}^m a_{ij} y_{ij} / \sum_{j=1}^m a_{ij}$, the cluster-specific weighted average of the response variable, $\bar{a}_{i.} = \sum_{j=1}^m a_{ij} / m$. It follows from (6) that

$$\mathbf{x}_i^T \hat{\boldsymbol{\beta}} + \tilde{b}_i = g \left(\bar{y}_{i.} - \frac{\tilde{b}_i \phi}{m \bar{a}_{i.} \theta} \right). \quad (9)$$

Pre-multiplying this expression by \mathbf{x}_i , summing over the index i , and recalling the constraint (7), it follows that

$$\hat{\boldsymbol{\beta}} = \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i g \left(\bar{y}_{i.} - \frac{\tilde{b}_i \phi}{m \bar{a}_{i.} \theta} \right). \quad (10)$$

Note that $\tilde{b}_i = \tilde{b}_i(\bar{y}_{i.}, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi / m \bar{a}_{i.})$.

We derive the asymptotic bias of $\hat{\boldsymbol{\beta}}$ using equation (10) assuming n is fixed and small while m goes to infinity. Our asymptotic calculations proceed by performing a series of Taylor expansions of $\bar{y}_{i.}$ about μ_i , \tilde{b}_i about b_i , and $\hat{\boldsymbol{\beta}}$ about $\boldsymbol{\beta}$. We state in the following Proposition the asymptotic bias and variance of the PQL estimator assuming n is fixed and small while m goes to infinity. We provide the proof in the Appendix.

Proposition 1 Assume the number of cluster n is fixed and small and the cluster size m goes to infinity. Suppose the variance component θ is known. The asymptotic bias and variance of the PQL estimators of the regression coefficients $\hat{\boldsymbol{\beta}}$ are

$$E(\hat{\boldsymbol{\beta}}) - \boldsymbol{\beta} = \frac{\phi}{m} \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \frac{1}{\bar{a}_{i.}} \mathbf{x}_i \mathbf{A}_i + O_p\left(\frac{1}{m^2}\right) \quad (11)$$

$$\text{cov}(\hat{\boldsymbol{\beta}}) = \theta \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} + \frac{\phi}{m} \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \mathbf{B} \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} + O_p\left(\frac{1}{nm^2}\right) \quad (12)$$

where

$$\begin{aligned} \mathbf{A}_i &= E_{b_i} \left[\frac{1}{2} v(\mu_i) g''(\mu_i) + \frac{1}{\theta} \left\{ \mathbf{x}_i^T \left(\sum_{i'=1}^n \mathbf{x}_{i'} \mathbf{x}_{i'}^T \right)^{-1} \mathbf{x}_i - 1 \right\} g'(\mu_i) b_i \right] \\ \mathbf{B} &= \sum_{i=1}^n \frac{1}{\bar{a}_{i.}} \mathbf{x}_i \mathbf{x}_i^T \left\{ E_{b_i} \left[v(\mu_i) \{g'(\mu_i)\}^2 \right] - \frac{2}{\theta} E_{b_i} \{g'(\mu_i) b_i^2\} \right\} \\ &\quad + \frac{2}{\theta} E_{b_i} \left\{ \left(\sum_{i=1}^n \mathbf{x}_i b_i \right) \left(\sum_{i=1}^n \frac{1}{\bar{a}_{i.}} \mathbf{x}_i \mathbf{x}_i^T g'(\mu_i) \right) \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \left(\sum_{i=1}^n \mathbf{x}_i^T b_i \right) \right\} \end{aligned}$$

These results show that in group-randomized trial settings when the number of clusters n is small and the cluster size m is large, the asymptotic bias of the PQL estimator $\hat{\beta}$ of the cluster level covariate effect is of order $O_p(m^{-1})$, which is small if m is large. This indicates that PQL works well for estimating the cluster level covariate effect in group-randomized trials. This result is considerably different from that of Breslow and Lin (1995), who considered the bias of the PQL estimator when the number of clusters n is large while the cluster size m is small. They found the PQL estimator is seriously biased for clustered binary data in such conventional longitudinal/clustered data settings.

Proposition 1 further shows that the variance of the PQL estimator of the cluster-level covariate effect, such as an intervention effect, is of order $O_p(1/n) + O_p\{1/(nm)\}$, which is of the same order as the maximum likelihood estimator in this small n large m situation. This result also suggests that in group randomized trials when n is fixed to be small, as expected, one often needs to have large cluster size m to achieve sufficient power to detect an intervention effect. Our simulation results in Section 4 further show that the finite sample variance and mean square error of the PQL estimator are smaller than that of the MLE. In view of the computational simplicity of PQL, this result is encouraging for the use of PQL to analyze data from grouped randomized trials.

Extension of the results in Proposition 1 to unbalanced designs where the cluster sizes vary from clusters to clusters is straightforward. Straightforward calculations show that one simply needs to remove m and replace \bar{a}_i by $\bar{a}_i m_i$ in both equations (11) and (12) and replace $O_p(m^{-2})$ by $O_p(\min(m_i)^2)$ and $O_p(\{(nm^2)^{-1}\})$ in equation (12) to $O_p[\{n\min^2(m_i)\}^{-1}]$.

4 SPECIAL CASES

We examine the general bias and variance expressions in two common clustered data settings. The first special case assumes an identity link function where expressions for the bias and variance associated with estimated cluster-level covariate effects have closed form solutions. We show the same bias expressions can be obtained directly from our general bias and variance expressions. The second special case considers the clustered data setting with a binary outcome where one is interested in the efficacy of, say, an intervention from a group-randomized trial.

4.1 IDENTITY LINK FUNCTION

We first consider a random effects model with an identity link function $g(\mu) = \mu$. Assume $a_{ij} = 1$. The bias and variance expression for estimating cluster-level covariates can be obtained from (11) and (12), respectively, noting in this case that $g'(\mu_i) = 1$ and $g''(\mu_i) = 0$. Thus,

$$\begin{aligned} E(\hat{\beta} - \beta) &= O_p(1/m^2), \\ \text{cov}(\hat{\beta}) &= \left(\theta + \frac{\phi E(v(\mu_i))}{m} \right) \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} + O_p(1/nm^2). \end{aligned}$$

The above results apply to both normal and non-normal outcomes when an identity link is used. If one further assumes that the outcome y_{ij} is normally distributed as $y_{ij} = \mathbf{x}_i^T \beta + b_i + e_{ij}$, where $b_i \sim N(0, \theta)$ and $e_{ij} \sim N(0, \phi)$, the above results become

$$\begin{aligned} E(\hat{\beta} - \beta) &= O_p(1/m^2), \\ \text{cov}(\hat{\beta}) &= \left(\theta + \frac{\phi}{m} \right) \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} + O_p(1/nm^2). \end{aligned}$$

one can easily show that in this case $O_p(1/m^2)$ and $O_p(1/nm^2)$ are zero. In other words, the above asymptotic bias and variance results are exact in the normal case. In this case, $\hat{\beta}$ is unbiased and the variance of the estimated cluster-level covariate effects is a function of both the within and between subject variation.

4.2 LOGIT LINK FUNCTION AND 2 GROUP COMPARISON

Now consider the special case where one is interested in the efficacy of an intervention in a group-randomized trial involving a binary outcome. Further, let $g(\mu_k) = \text{logit}(\mu_k)$ where μ_k is the probability of a positive response for a randomly selected individual in the k th group ($k = 1, 2$), conditional on the value of the individual's random effect. Note that while technically μ_k depends on b , we suppress this for notational simplicity.

Under this convention,

$$\text{logit}(\mu_1) = \beta_0 + b \text{ and } \text{logit}(\mu_2) = \beta_0 + \beta_1 + b,$$

where $b \sim \text{Normal}(0, \theta)$. The first and second derivatives of $g(\mu_k)$ with respect to μ_k are,

$$g'(\mu_k) = \frac{1}{\mu_k(1 - \mu_k)} \quad \text{and} \quad g''(\mu_k) = \frac{-(1 - 2\mu_k)}{[\mu_k(1 - \mu_k)]^2}.$$

Now define \mathbf{x}_k (a 2×1 vector) where $\mathbf{x}_k = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$ for clusters in the control group ($k = 1$) and $\mathbf{x}_k = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$ for clusters in the treatment group ($k = 2$). Finally, denote the number of clusters for the control and treatment groups as n_1 and n_2 , respectively, with $n = n_1 + n_2$ (total number of clusters). Define $\gamma = n_2/n$ (the proportion of clusters in the treatment group or randomization fraction). Some calculations using (11) show that the asymptotic bias of the PQL estimator $\hat{\beta}$ is

$$E(\hat{\beta}) - \beta = \frac{1}{m} \begin{pmatrix} S_1 \\ S_2 - S_1 \end{pmatrix} + O_p(m^{-2}), \quad (13)$$

where for $j = 1, 2$,

$$S_j = E_b \left\{ \frac{-(1 - 2\mu_j)}{2\mu_j(1 - \mu_j)} \right\} + \left(\frac{1}{n_j} - 1 \right) E_b \left\{ \frac{b}{\mu_j(1 - \mu_j)} \right\}$$

The variance expression is complicated and is omitted here.

Equation (13) illustrates that the bias decreases as the cluster-size increases. For a fixed cluster-size, the magnitude depends on baseline event rate (reflected through S_1) as well as the true difference in the event rates for treated and control groups ($S_2 - S_1$). The randomization fraction γ , does not influence the magnitude of bias as reflected in equation (13). The variance in this setting is also a function of the cluster-size and will decrease as the cluster-size increases (for fixed n). Calculations using equation (12) show that the variance is influenced by the randomization fraction γ .

5 SIMULATION STUDY

We conducted a simulation study to examine the theoretical and empirical bias and variance of PQL compare them with the MLE in estimating covariate effects at the cluster level under the logit link function for settings with small numbers of large clusters. We generated a common random effect for each of the $i = 1, \dots, n$ clusters (b_i) from a Normal($0, \theta$) distribution and conditional on the random effect, a single Bernoulli random variable was generated from the following model:

$$y_{ij} = \text{Bernoulli}(\mu_i) \text{ where } \mu_i = \frac{\exp(\beta_0 + \beta_1 x_i + b_i)}{1 + \exp(\beta_0 + \beta_1 x_i + b_i)}. \quad (14)$$

In this model, x_i is a single cluster-level covariate assumed to follow a Normal($1, 1$) distribution.

In our simulation study $\beta_0 = 1.5$, $\beta_1 = -1.2$ and $\theta = 0.5$.

For each simulated dataset, we estimated $\beta = (\beta_0, \beta_1)^T$ using the PQL estimator via the SAS GLIMMIX macro as well as the MLE using the SAS NLMIXED procedure. In both the PQL and NLMIXED approaches, we estimated β assuming θ was fixed and known ($\theta = 0.5$) as well as assuming θ was unknown. Whereas the PQL approach is based on the Laplace approximation to the loglikelihood function, NLMIXED approximates the marginal loglikelihood function (3) numerically (e.g., Gaussian quadrature) and finds MLEs for the parameters of interest via Newton Raphson. Variance estimates from the NLMIXED procedure are obtained from the appropriate function of the Hessian matrix at the final step of Newton Raphson. Simulation results are presented in the Tables 1 and 2 and Figures 1-3 and the summaries are restricted to characterizing only the results of β_1 .

Table 1 summarizes the empirical results from all simulation scenarios considered ($n=6, 10, 20$ and 50 clusters of size $m=10, 20, 50$ and 100) assuming θ is both fixed and known, while Table 2 provide the results for the same settings when θ is unknown and estimated. Figure 1 compares the empirical biases of the PQL and MLE estimators of cluster-level covariate effects with the theoretical bias defined in equation (11) assuming θ is both fixed and known as well as for θ unknown; and Figures 2 and 3 compare the empirical SEs and MSEs of $\hat{\beta}$ using the MLE and PQL methods assuming θ is known and unknown.

We first examine the empirical bias properties of each estimation method. The results in Tables 1 and 2 and Figure 1 show that in practical group randomized trial settings with a small number clusters and moderate to large cluster size cluster size, the PQL estimate had small bias. In fact, PQL (REML and ML) did generally perform better than the MLE in settings typical of group randomized trials (e.g., 6 and 10 clusters in Figure 1). Also, the empirical PQL bias (REML and ML) was similar (relatively and in absolute value) to its theoretical approximations presented in this paper, especially in settings where there are few clusters which are typical settings for group randomized trials. The theoretical bias (Figure 1) seems to suggest that the bias associated with PQL (ML and REML) cluster-level covariate effects is negligible in each of the settings considered in the simulation study (e.g., the theoretical bias curve approaches the zero horizontal line in each setting presented in Figure 1), but practically the PQL bias only seems to reach the zero horizontal line when there were only 6 clusters possibly suggesting that the theoretical estimates may be an

overly optimistic practical result, except in the setting most typical of group randomized trials (e.g., a small number of clusters). Finally, the MLE has the smallest bias in settings where there are large numbers of clusters (20 and 50 clusters), as expected.

Tables 1 and 2 also contain the average estimated mean square error (MSE) for each method of estimation. The PQL MSE is smaller than the MLE MSE in each simulation setting considered. In settings where θ was assumed to be known, the magnitude of the difference between the average MSE between PQL and MLE was greater in settings with a few clusters (e.g., 6 and 10 clusters), but the difference becomes negligible as the number of clusters increases (e.g., 20 and 50 clusters). However, regardless of the number of clusters, the MSE for each of the three estimation methods decreased as the cluster size increased. We observed similar results in settings when θ was estimated. Specifically, the average MSE summarized in Table 2 suggests that the MSE associated with each of the three estimation methods are similar in all the simulation settings considered when θ is unknown and that, in general, PQL (ML) has modestly superior MSE properties when compared to the other methods.

Figures 2 and 3 characterize the empirical standard errors and MSEs associated with estimating cluster-level covariate effects using PQL and MLE. The results also show that SE efficiency and MSE efficiency of all three methods was indistinguishable when θ was assumed fixed and known or when θ was estimated. The PQL estimates have a light improvement in SEs and MSEs over the MLEs..

We also compared the computing resources required for the PQL approach versus the MLE using the SAS NLMIXED procedure to see if there would be big differences in computing resources and times for the two approaches. Although NLMIXED had comparable results (average parameter estimates, estimated standard errors, etc.), we found the procedure to be more computationally intensive and greatly increased the total computing time for modeling the same datasets when compared to fitting equivalent PQL models. For example, the CPU for modeling a single simulated dataset with 10 clusters and 100 responses per cluster was approximately 5 times greater using the NLMIXED procedure than the PQL approach (NLMIXED = 15.64 seconds and PQL = 3.47 seconds). This additional CPU time is likely due to the Newton Raphson algorithm which involves inverting a matrix whose dimension depends on the number of independent responses within

clusters. Because of this matrix inversion step in the modeling algorithm, this method may be unstable if the matrix to be inverted is singular or computationally intensive if the matrix is large. So one may want to consider the trade-off in CPU time and bias in estimating covariate effects of interest associated with fitting the more computationally intense random effects models using the NLMIXED procedure versus using the PQL approach.

6 DISCUSSION

The PQL approach has been shown to produce biased estimates of covariate effects in clustered data settings with small numbers of observations per cluster or in settings with large variance components. Our early empirical results show that this bias may be small compared to MLEs in common group-randomized settings (small numbers of large clusters). In this paper, we have shown theoretically and in a simulation study that the bias in estimating cluster-level covariate effects using the PQL method is inversely proportional to the cluster-size. This result has important implications, especially in the context of community-based studies which typically have small numbers of large clusters. The results presented here suggest that the bias in estimating covariate effects at the cluster-level via PQL can be minimized to an extent in settings where the number of independent clusters may be small and/or fixed (e.g., number of census block-groups in a school district of interest) by sampling more subjects within clusters. We have also shown that the variance associated with these estimates is inversely proportional to the total number of clusters. Additionally, the variance is a function of both the between and within subject variability as well as the cluster size. We have found in our simulation study that the MSEs of the PQL estimates are slightly smaller than the MLE counterparts in practical group-randomized trial settings. We have presented main results both theoretically and from simulation studies for equal cluster-sizes, but have generalized our results unequal cluster size settings at the end of Section 3.

An alternative method to estimate the regression coefficients is to use a two-stage method. Although the two-stage method is simple, it has several major limitations. One would not be able to perform a two-stage analysis for cluster-level covariates, the main interest in the current paper. Second, inference in two-stage analysis is difficult since one has to account for variability in estimation of both stages. Fitzmaurice, Laird and Ware (2004) note their discussion of the

two-stage random effects model formulation is for pedagogical purposes, and caution readers that such a formulation, although helpful conceptually, introduces extraneous and sometimes impractical model restrictions.

We focus in this paper on studying the asymptotic bias of the regression coefficients of cluster-level covariates in group-randomized trial settings with a small number of clusters and large cluster sizes. We assume the variance component θ is known in our calculations. In practice the variance component is often unknown. The theoretical results for quantifying the bias of covariate effects when θ is unknown is beyond the scope of this paper, and is of significant interest for future research. Our simulation study results suggest that in typical group-randomized trial settings, the practical implication of assuming θ is known and fixed vs settings where θ is estimated are negligible even in settings with small numbers of clusters, given a reasonable cluster size (e.g., cluster size ≥ 20). Although we have not presented theoretical arguments exploring a relaxation of this assumption, our simulation studies may give some practical insight on how the results might compare in settings where θ is unknown.

Another area of future research is to study the asymptotic bias of the regression coefficients of subject-level covariates in settings with a small number of clusters and large cluster sizes. This would require developing a different asymptotic analytic technique and would be of future research interests.

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Appendix 1: Proof of Proposition 1

From equation (9), we can write \tilde{b}_i as $\tilde{b}_i = h(\bar{y}_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m)$, where $h(\cdot)$ is the solution to (9).

Then the PQL estimator $\hat{\boldsymbol{\beta}}$ can be written as

$$\hat{\boldsymbol{\beta}} = \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i g \left\{ \bar{y}_i - h(\bar{y}_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right\}.$$

We first expand \bar{y}_i in $h(\cdot)$ about μ_i as

$$\begin{aligned} \hat{\boldsymbol{\beta}} &= \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i \left[g \left\{ \mu_i - h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right\} \right. \\ &+ (\bar{y}_i - \mu_i) g' \left(\mu_i - h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right) \left(1 - h'_{\mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right) \\ &+ \frac{(\bar{y}_i - \mu_i)^2}{2!} \left\{ g' \left(\mu_i - h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right) \left(-h''_{\mu_i \mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right) \right. \\ &\quad \left. + \left(1 - h'_{\mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right)^2 g'' \left(\mu_i - h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} \right) \right\} \\ &+ O_p(1/m^2), \end{aligned}$$

where $h'_{\mu_i}(\cdot) = \partial h(\cdot) / \partial \mu_i$ and $h''_{\mu_i \mu_i}(\cdot) = \partial^2 h(\cdot) / \partial \mu_i \partial \mu_i$. Next, a further expansion of $g(\cdot)$ about $g(\mu_i)$ gives

$$\begin{aligned} \hat{\boldsymbol{\beta}} &= \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i \left\{ g(\mu_i) - h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \frac{\phi}{m \bar{a}_i \theta} g'(\mu_i) \right. \\ &+ (\bar{y}_i - \mu_i) \left[g'(\mu_i) - \frac{\phi}{m \bar{a}_i \theta} \left\{ h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) g''(\mu_i) + g'(\mu_i) h'_{\mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \right\} \right] \\ &+ \frac{(\bar{y}_i - \mu_i)^2}{2} \left[g''(\mu_i) - \frac{\phi}{m \bar{a}_i \theta} \left\{ h(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) g'''(\mu_i) + g'(\mu_i) h''_{\mu_i \mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \right. \right. \\ &\quad \left. \left. + 2g''(\mu_i) h'_{\mu_i}(\mu_i, \mathbf{x}_i^T \hat{\boldsymbol{\beta}}, \phi, \theta, 1/m) \right\} \right] \left. \right\} + O_p(1/m^2), \end{aligned}$$

Next expand $\hat{\boldsymbol{\beta}}$ in $h(\cdot)$ about $\boldsymbol{\beta}$ and use the fact $g(\mu_i) = \mathbf{x}_i^T \boldsymbol{\beta} + b_i$, some calculations give

$$\hat{\boldsymbol{\beta}} = \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i (\mathbf{x}_i^T \boldsymbol{\beta} + d_i) + O_p(1/m^2) + O_p(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})^2 - \frac{\phi}{m\theta} \mathbf{K}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}),$$

where

$$\begin{aligned}
d_i &= \left[b_i - \frac{\phi}{m\bar{a}_i\theta} g'(\mu_i) h_i(\cdot) \right. \\
&+ (\bar{y}_i - \mu_i) \left[g'(\mu_i) - \frac{\phi}{m\bar{a}_i\theta} \{g''(\mu_i) h_i(\cdot) + g'(\mu_i) h'_{\mu_i}(\cdot)\} \right] \\
&+ \frac{1}{2} (\bar{y}_i - \mu_i)^2 \left[g''(\mu_i) - \frac{\phi}{m\bar{a}_i\theta} \{g'''(\mu_i) h_i(\cdot) + g'(\mu_i) h''_{\mu_i\mu_i}(\cdot) + 2g''(\mu_i) h'_{\mu_i}(\cdot)\} \right]
\end{aligned}$$

(\cdot) denotes $(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m)$, \mathbf{K} is the following $p \times p$ matrix (e.g., the first derivative terms wrt $\boldsymbol{\beta}$ from the previous expression),

$$\mathbf{K} = \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \frac{1}{\bar{a}_i} \mathbf{x}_i \mathbf{c}_i^T$$

where

$$\begin{aligned}
\mathbf{c}_i &= g'(\mu_i) h'_{i\beta}(\cdot) + (\bar{y}_i - \mu_i) \{g'(\mu_i) h''_{i\mu_i\beta}(\cdot) + g''(\mu_i) h'_{i\beta}(\cdot)\} \\
&+ \frac{1}{2} (\bar{y}_i - \mu_i)^2 \{h'_{i\beta}(\cdot) g'''(\mu_i) + h'''_{i\mu_i\mu_i\beta}(\cdot) g'(\mu_i) + 2h''_{i\mu_i\beta}(\cdot) g''(\mu_i)\},
\end{aligned}$$

and $h'_{i\beta}(\cdot)$, $h''_{i\mu_i\beta}(\cdot)$ and $h'''_{i\mu_i\mu_i\beta}(\cdot)$ denote the derivatives of $h_i(\cdot)$, $h'_{\mu_i}(\cdot)$ and $h''_{\mu_i\mu_i}(\cdot)$ with respect to $\boldsymbol{\beta}$ and (\cdot) denotes $(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m)$. Using $g(\mu_i) = \mathbf{x}_i^T \boldsymbol{\beta} + b_i$ and collecting $\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}$ terms,

$$\begin{aligned}
\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta} &= \left(\mathbf{I} + \frac{\phi}{m\theta} \mathbf{K} \right)^{-1} \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i d_i + O_p(1/m^2) \\
&= \left(\mathbf{I} - \frac{\phi}{m\theta} \mathbf{K} \right) \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \sum_{i=1}^n \mathbf{x}_i d_i + O_p(1/m^2) \\
&= \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \left(\sum_{i=1}^n \mathbf{x}_i d_i \right) \\
&\quad - \frac{\phi}{m\theta} \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \left(\sum_{i=1}^n \frac{1}{\bar{a}_i} \mathbf{x}_i \mathbf{c}_i^T \right) \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \right)^{-1} \left(\sum_{i=1}^n \mathbf{x}_i d_i \right) + O_p(1/m^2),
\end{aligned}$$

where \mathbf{I} is the $p \times p$ identity matrix.

Now examine $h_i(\cdot) = h(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \theta, 1/m)$ and $h_{i\beta}(\cdot) = \partial h(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \theta, 1/m) / \partial \boldsymbol{\beta}$. We show in Appendix 2 that $h_i(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \theta, 1/m) = b_i + O_p(1/m)$, and in Appendix 3 that $h_{i\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \theta, 1/m) = -\mathbf{x}_i^T + O_p(1/m)$. Plugging $h_i(\cdot)$ by b_i in d_i and $h'_{i\beta}(\cdot)$ by $-\mathbf{x}_i^T$ in \mathbf{c}_i^T , and noticing $E\{g'(\mu_i) b_{i'}\} = E\{g'(\mu_i) b_i\}$ if $i = i'$ and 0 otherwise, keeping the terms of order $O_p(1/m)$, some calculations give the bias and variance expressions in (11) and (12).

Appendix 2: Proof of $h_i(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m) = b_i + O_p(1/m)$

By definition $h(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \theta, 1/m)$ is the solution for \tilde{b}_i of the equation,

$$\begin{aligned}\mu_i - g^{-1}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &= \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta} \\ \mu_i - \mu(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &= \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta},\end{aligned}\tag{15}$$

where $\mu(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) = g^{-1}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i)$. Expanding the left side of the above equation in a first order Taylor series about b_i , we get the following expression:

$$\begin{aligned}\mu_i - \mu(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &\approx \mu_i - \left\{ \mu(\mathbf{x}_i^T \boldsymbol{\beta} + b_i) + (\tilde{b}_i - b_i) \mu'(\mathbf{x}_i^T \boldsymbol{\beta} + b_i) \right\} = \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta} \\ \mu_i - \mu_i - (\tilde{b}_i - b_i) \mu'(\mathbf{x}_i^T \boldsymbol{\beta} + b_i) &= \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta}.\end{aligned}$$

Solving this expression for \tilde{b}_i ,

$$\tilde{b}_i = b_i \left(\frac{\mu'(\mathbf{x}_i^T \boldsymbol{\beta} + b_i)}{\mu'(\mathbf{x}_i^T \boldsymbol{\beta} + b_i) + \frac{\phi}{m \bar{a}_i \theta}} \right).$$

For large m , one can easily show from this equation

$$\tilde{b}_i = b_i + O_p(1/m).$$

Appendix 3: Proof of $h'_{i\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m) = -\mathbf{x}_i^T + O_p(1/m)$.

By definition

$$\begin{aligned}\mu_i - g^{-1}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &= \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta} \\ \mu_i - \mu(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &= \frac{\tilde{b}_i \phi}{m \bar{a}_i \theta}.\end{aligned}\tag{16}$$

Taking derivatives of (16) wrt $\boldsymbol{\beta}$,

$$\begin{aligned}- (\mathbf{x}_i^T + h'_{i\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m)) \mu'_{\beta}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i) &= \frac{h'_{\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m)}{m \theta} \\ h'_{i\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m) &= -\mathbf{x}_i^T \left(\frac{\mu'_{\beta}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i)}{\frac{\phi}{m \bar{a}_i \theta} + \mu'_{\beta}(\mathbf{x}_i^T \boldsymbol{\beta} + \tilde{b}_i)} \right).\end{aligned}$$

As m gets large, $h'_{i\beta}(\mu_i, \mathbf{x}_i^T \boldsymbol{\beta}, \phi, \theta, 1/m) = -\mathbf{x}_i^T + O_p(1/m)$.

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Table 1: Simulation study results (from 500 simulated samples) summarizing estimated cluster-level covariate effects from the logistic-normal model characterized in (14) for θ known. (True population parameters: $\beta = -1.2$ and $\theta = 0.5$.)

	PQL			MLE		
	avg $\hat{\beta}$ (SD $\hat{\beta}$)	avg SE $\hat{\beta}$	avg MSE	avg $\hat{\beta}$ (SD $\hat{\beta}$)	avg SE $\hat{\beta}$	avg MSE
6 Clusters						
Cluster size = 10	-1.351 (0.868)	0.673	1.526	-1.427 (0.915)	0.683	1.723
Cluster size = 20	-1.228 (0.596)	0.520	0.710	-1.282 (0.622)	0.525	0.781
Cluster size = 50	-1.212 (0.487)	0.451	0.474	-1.244 (0.502)	0.453	0.505
Cluster size = 100	-1.199 (0.442)	0.404	0.390	-1.218 (0.451)	0.405	0.406
10 Clusters						
Cluster size = 10	-1.223 (0.431)	0.439	0.372	-1.293 (0.456)	0.446	0.424
Cluster size = 20	-1.203 (0.378)	0.359	0.286	-1.255 (0.396)	0.362	0.316
Cluster size = 50	-1.194 (0.307)	0.299	0.188	-1.225 (0.317)	0.300	0.202
Cluster size = 100	-1.189 (0.284)	0.279	0.161	-1.208 (0.290)	0.279	0.168
20 Clusters						
Cluster size = 10	-1.137 (0.273)	0.280	0.153	-1.202 (0.289)	0.285	0.167
Cluster size = 20	-1.159 (0.234)	0.233	0.111	-1.208 (0.245)	0.236	0.120
Cluster size = 50	-1.192 (0.196)	0.201	0.076	-1.223 (0.202)	0.202	0.082
Cluster size = 100	-1.185 (0.180)	0.184	0.065	-1.205 (0.184)	0.184	0.068
50 Clusters						
Cluster size = 10	-1.139 (0.166)	0.170	0.059	-1.204 (0.176)	0.172	0.062
Cluster size = 20	-1.168 (0.138)	0.143	0.039	-1.218 (0.145)	0.144	0.042
Cluster size = 50	-1.170 (0.115)	0.122	0.027	-1.200 (0.119)	0.123	0.028
Cluster size = 100	-1.172 (0.110)	0.113	0.025	-1.191 (0.113)	0.113	0.026

Table 2: Simulation study results (from 500 simulated samples) summarizing estimated cluster-level covariate effects from the logistic-normal model characterized in (14) for unknown θ . (True population parameters: $\beta = -1.2$ and $\theta = 0.5$.)

	PQL (ML)			PQL (REML)			MLE		
	avg $\hat{\beta}$ (SD $_{\hat{\beta}}$)	avg SE $_{\hat{\beta}}$	avg MSE	avg $\hat{\beta}$ (SD $_{\hat{\beta}}$)	avg SE $_{\hat{\beta}}$	avg MSE	avg $\hat{\beta}$ (SD $_{\hat{\beta}}$)	avg SE $_{\hat{\beta}}$	avg MSE
6 Clusters									
Cluster size = 10	-1.359 (0.890)	0.581	1.608	-1.396 (0.942)	0.686	1.813	-1.386 (0.895)	0.625	1.635
Cluster size = 20	-1.221 (0.593)	0.414	0.702	-1.238 (0.605)	0.488	0.734	-1.245 (0.605)	0.432	0.897
Cluster size = 50	-1.209 (0.492)	0.363	0.483	-1.221 (0.497)	0.437	0.494	-1.223 (0.501)	0.373	0.503
Cluster size = 100	-1.193 (0.439)	0.325	0.386	-1.200 (0.442)	0.394	0.390	-1.207 (0.445)	0.331	0.396
10 Clusters									
Cluster size = 10	-1.237 (0.449)	0.404	0.404	-1.256 (0.460)	0.446	0.425	-1.278 (0.464)	0.435	0.436
Cluster size = 20	-1.204 (0.385)	0.316	0.296	-1.217 (0.390)	0.350	0.304	-1.239 (0.398)	0.333	0.318
Cluster size = 50	-1.191 (0.308)	0.264	0.190	-1.199 (0.311)	0.294	0.193	-1.216 (0.315)	0.273	0.198
Cluster size = 100	-1.186 (0.282)	0.245	0.160	-1.191 (0.284)	0.272	0.161	-1.202 (0.287)	0.249	0.164
20 Clusters									
Cluster size = 10	-1.144 (0.284)	0.262	0.164	-1.152 (0.286)	0.275	0.166	-1.193 (0.297)	0.282	0.177
Cluster size = 20	-1.158 (0.236)	0.215	0.113	-1.164 (0.237)	0.226	0.114	-1.199 (0.245)	0.227	0.120
Cluster size = 50	-1.191 (0.196)	0.187	0.077	-1.195 (0.197)	0.196	0.078	-1.219 (0.202)	0.193	0.082
Cluster size = 100	-1.183 (0.181)	0.170	0.066	-1.186 (0.181)	0.179	0.066	-1.202 (0.185)	0.173	0.068
50 Clusters									
Cluster size = 10	-1.143 (0.170)	0.161	0.061	-1.147 (0.171)	0.164	0.061	-1.200 (0.181)	0.175	0.065
Cluster size = 20	-1.169 (0.139)	0.136	0.039	-1.172 (0.139)	0.139	0.040	-1.216 (0.145)	0.144	0.042
Cluster size = 50	-1.169 (0.115)	0.117	0.028	-1.170 (0.116)	0.120	0.028	-1.198 (0.119)	0.121	0.028
Cluster size = 100	-1.170 (0.111)	0.108	0.025	-1.172 (0.111)	0.111	0.025	-1.189 (0.113)	0.111	0.026

Figures

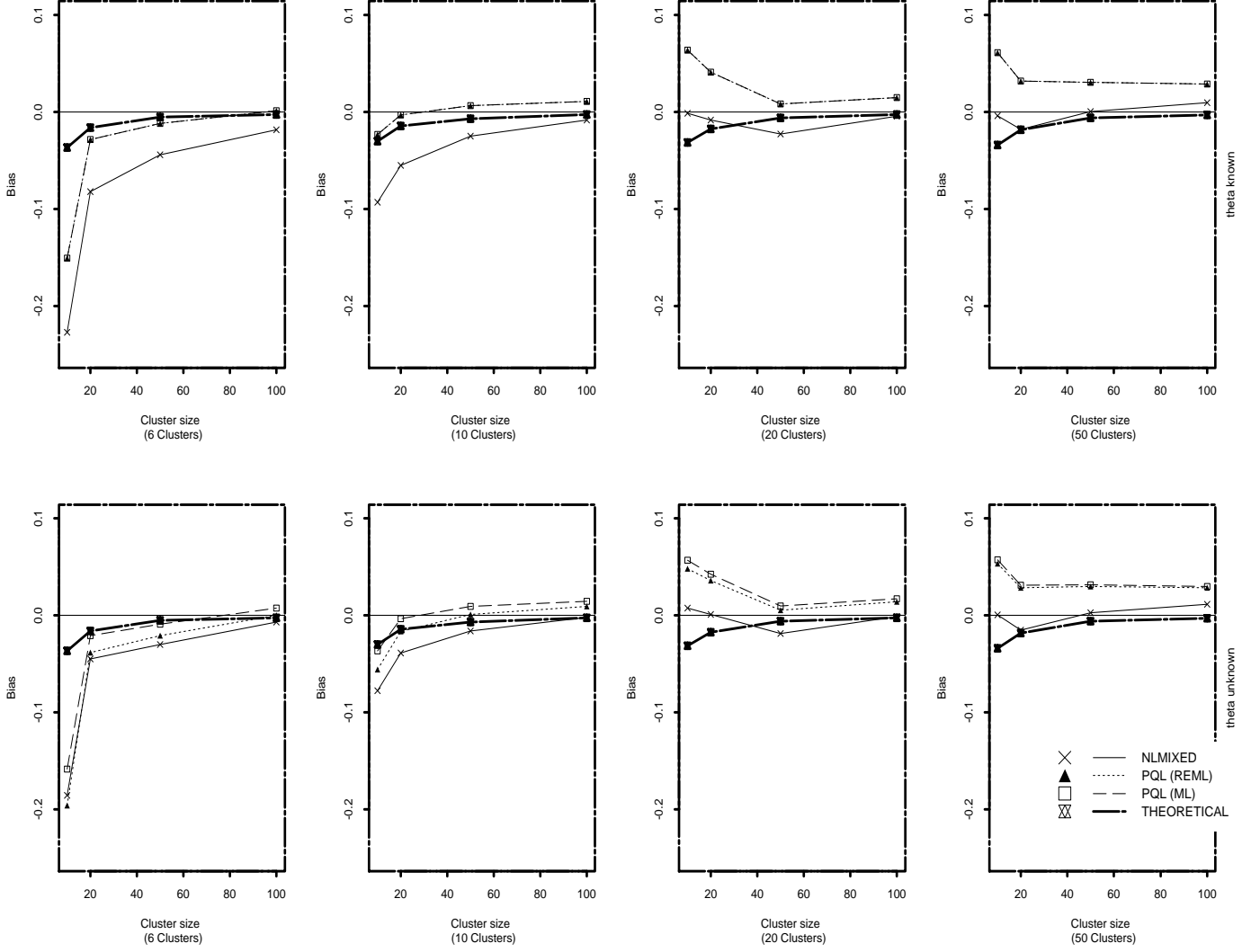


Figure 1: Average bias in estimating cluster-level covariate effects from the logistic mixed model (14) via penalized quasi-likelihood (PQL (REML) and PQL (ML)), MLE, theoretical bias of the PQL estimate from the analytic asymptotic bias expression in equation (11) (THEORETICAL) for θ known (top row) and θ unknown (bottom row).

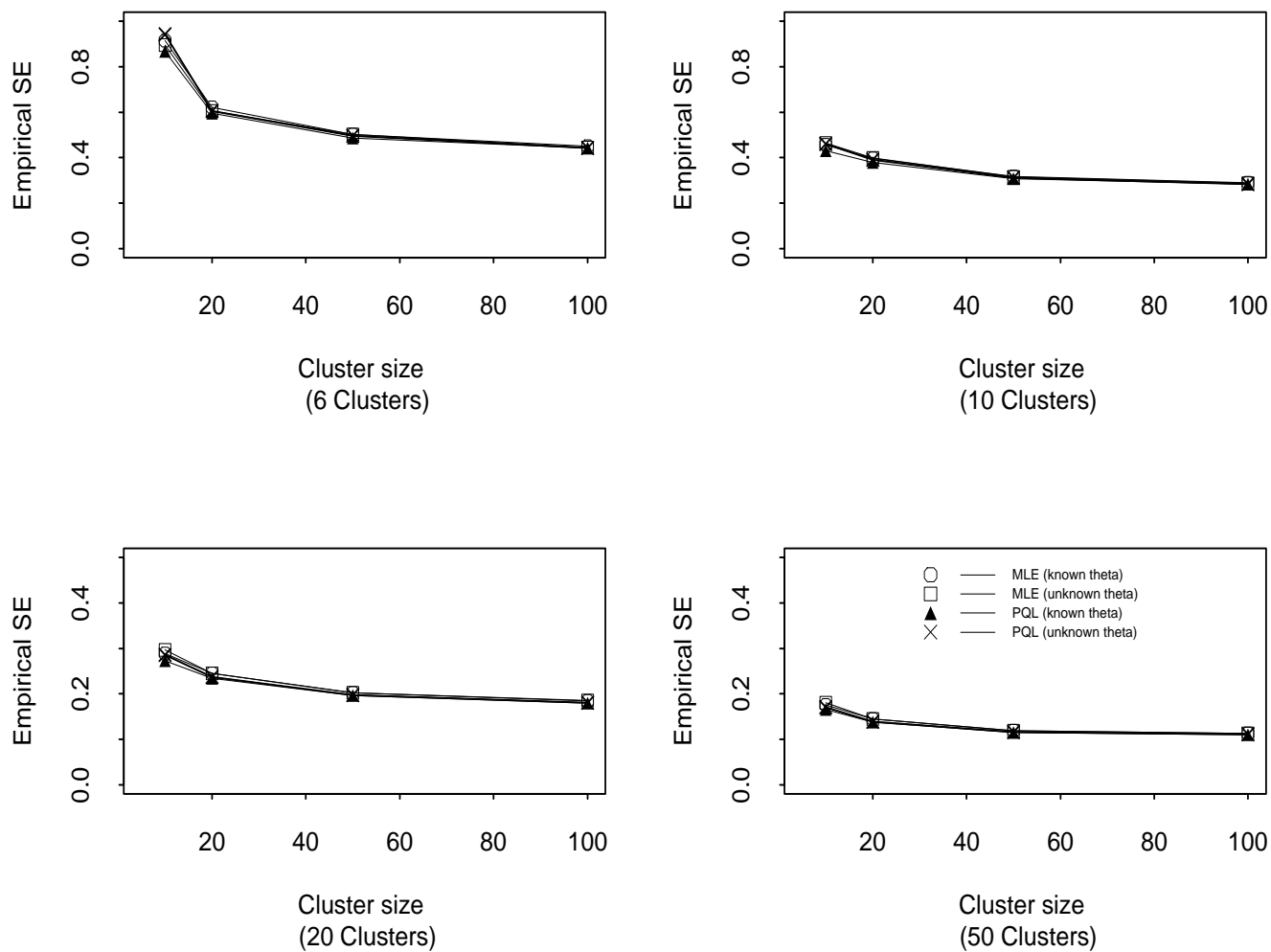


Figure 2: Comparison of empirical SEs for estimated cluster-level covariate effects from the logistic mixed model (14) via penalized quasi-likelihood (PQL) and the MLE assuming θ is known and unknown.

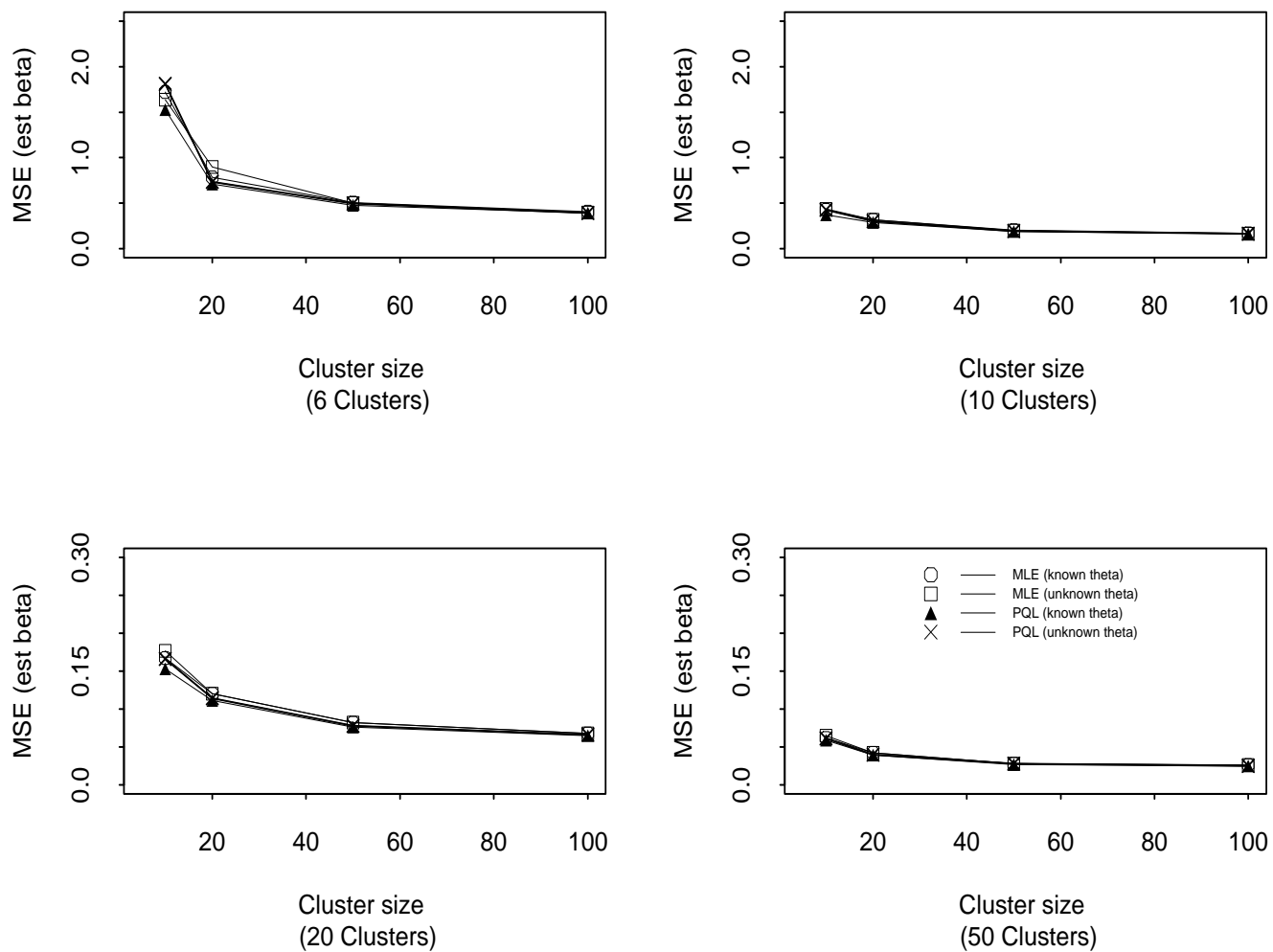


Figure 3: Comparison of MSEs for estimated cluster-level covariate effects from the logistic mixed model (14) via penalized quasi-likelihood (PQL) and the MLE assuming θ is known and unknown.