An Empirical Likelihood Approach to Nonparametric Covariate Adjustment in Randomized Clinical Trials

Xiaoru Wu and Zhiliang Ying

Covariate adjustment is an important tool in the analysis of randomized clinical trials and observational studies. It can be used to increase efficiency and thus power, and to reduce possible bias. While most statistical tests in randomized clinical trials are nonparametric in nature, approaches for covariate adjustment typically rely on specific regression models, such as the linear model for a continuous outcome, the logistic regression model for a dichotomous outcome and the Cox model for survival time. Several recent efforts have focused on model-free covariate adjustment. This paper makes use of the empirical likelihood method and proposes a nonparametric approach to covariate adjustment. A major advantage of the new approach is that it automatically utilizes covariate information in an optimal way without fitting nonparametric regression. The usual asymptotic properties, including the Wilks-type result of convergence to a $\chi^2$ distribution for the empirical likelihood ratio based test, and asymptotic normality for the corresponding maximum empirical likelihood estimator, are established. It is also shown that the resulting test is asymptotically most powerful and that the estimator for the treatment effect achieves the semiparametric efficiency bound. The new method is applied to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-I trial. Extensive simulations are conducted, validating the theoretical findings.

KEY WORDS: Estimating Equation; Likelihood Ratio Test; Semiparametric Efficiency; Wilks Theorem.

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1. INTRODUCTION

Testing for the statistical significance of treatment differences is a key element in the analysis of randomized clinical trials. In its simplest form, patients are randomly allocated to either a treatment or control group and their responses are recorded. Many statistical methods are available for testing whether there is convincing evidence that a treatment difference exists between the two groups; cf. Pocock (1983) and Friedman, Furberg and DeMets (1998). In addition to treatment allocation and outcome values, baseline covariate information is often collected in such clinical studies. Classical analysis of covariance (ANCOVA) and other regression model-based tests may be used to handle covariate adjustment; cf. Scheffe (1959), Simon (1984), McCullagh and Nelder (1989) and Rutter and Elashoff (1994). When properly used, covariate adjustment can increase efficiency and, in the case of an observational study, reduce bias (Armitage 1981).

Due to randomization, most two-sample (multi-sample if more than two treatment groups are involved) tests are valid without any parametric assumption. Therefore, these tests are nonparametric in nature, a feature of great importance in a clinical trial. Standard methods for covariate adjustment, however, require that a specific regression model be assumed; see, for example, Piantadosi (2005, Chapter 17).

Adjusting for covariates without assuming a regression model has been studied by Koch (1998), Tsiatis, Davidian, Zhang and Lu (2008) among others. In particular, Koch (1998) proposed a weighted least squares method to include covariate information for estimating the treatment difference. This method always leads to a variance reduction, thus an increase in power. By appealing to semiparametric efficiency theory, Tsiatis et al. (2008) developed a general approach to covariate adjustment that circumvents modeling the covariate-outcome relationship. Their approach allows for nonlinear terms in relating the auxiliary covariates to the outcome variable, thereby further reducing the variability. They showed that the method is semiparametrically efficient by deriving the semiparametric information bound and by showing the bound is attained with their approach.
An essential ingredient in the approach by Tsiatis et al. (2008) is the use of the independence of treatment allocation and baseline covariates to construct equations associated. These equations can be viewed as constraints that, when properly utilized, may lead to further reduction in variability of the outcome variable. How to optimally use these constraints is therefore crucial for efficiency improvement.

Empirical likelihood (Owen 1988) is a general method for efficiently utilizing constraints or estimating equations. Specifically, it maximizes the nonparametric likelihood (Kiefer and Wolfowitz 1956) subject to certain constraints that are specific to the problem of interest. It can be used to obtain empirical likelihood ratio tests as well as confidence intervals. Examples include testing and interval estimation for population means and for regression coefficients. Qin and Lawless (1994) showed that the constraints can be used more liberally in the sense that the number of constraints may exceed the number of parameters of interest. They also showed that the empirical likelihood utilizes the information in the constraints in an optimal way.

Because baseline covariate information for a randomized clinical trial generates constraints, it is natural to consider the empirical likelihood as a means to improve efficiency for the primary problem of testing and estimating treatment difference. To that end, this paper proposes a general approach to covariate adjustment by making use of the empirical likelihood and suitably choosing constraints. The new approach does not require any model assumption on the relationship between the outcome variable and baseline covariates. It is shown that such an empirical likelihood based method automatically results in efficiency improvement. For testing, it is asymptotically most powerful; for estimation, it achieves the semiparametric information bound.

The rest of the paper is organized as follows. In Section 2 we introduce some notation and briefly discuss existing model-based methods. We apply the empirical likelihood method for covariate adjustment and extend it to inference with growing number of constraints in Section 3. The design and results of simulation studies are described in Section 4. In Section 5, the method is applied to a study of acute myocardial infarction. Some concluding remarks are given in Section 6.
2. NOTATION AND MODEL SPECIFICATION

In a $(K + 1)$-arm $(K \geq 1)$ randomized clinical trial, for subject $i$, let $Y_i$, $Z_i$ and $X_i$ denote the outcome, treatment allocation and available auxiliary baseline covariates, respectively. Assume that $(Y_i, Z_i, X_i), i = 1, \ldots, n$, are independent and identically distributed (i.i.d.) and that the random allocation probabilities $\pi_k = P(Z = k), k = 0, \ldots, K$, where $\sum_{k=0}^{K} \pi_k = 1$, are known.

Throughout, $G^k$ denotes the conditional distribution of the outcome variable $Y$ given treatment allocation $Z = k, k = 0, \ldots, K$. Then the usual null hypothesis of no treatment difference is given by

$$H_0 : G^0 = G^1 = \ldots = G^K.$$

Note that there is no assumption on the form of $\{G^k, k = 0, \ldots, K\}$.

To study treatment effects, one may choose certain contrasts among the treatment groups in terms of their population characteristics, for example, the difference in mean outcomes between two treatment groups. Following Zhang et al. (2008), the treatment effect can be identified by considering

(1) \[ \beta_1 = E(Y|Z = 0), \quad \beta_2 = E(Y|Z = 1) - E(Y|Z = 0), \]

or equivalently, by formulating

(2a) \[ E(Y|Z) = \beta_1 + \beta_2 Z. \]

Clearly, such an approach does not require model assumption on the underlying distribution functions $G^k, k = 0, \ldots, K$. If there are more than two treatment groups, equation (2a) becomes

(2b) \[ E(Y|Z) = \beta_1 + \beta_2 1_{(Z=1)} + \ldots + \beta_{K+1} 1_{(Z=K)}, \]

where $1_{(\cdot)}$ is the indicator function and $\beta_{k+1}$ represents the difference in mean outcome between group $k$ and group 0. For a binary outcome, an alternative formulation is via the log-odds ratios:

(3) \[ \text{logit}\{P(Y = 1|Z)\} = \log \left\{ \frac{P(Y = 1|Z)}{P(Y = 0|Z)} \right\} = \beta_1 + \beta_2 1_{(Z=1)} + \ldots + \beta_{K+1} 1_{(Z=K)}. \]
Under this formulation, testing the null hypothesis of no treatment difference is tantamount to testing $H_0: \beta_2 = \ldots = \beta_{K+1} = 0$, and estimating the treatment effect is tantamount to estimating values of the $\beta_k, k = 2, \ldots, K + 1$. For notational convenience, we use $\beta$ to denote the parameter vector $(\beta_1, \ldots, \beta_{K+1})^T$.

Besides the outcome variable and treatment assignment, relevant baseline covariates, which may comprise patients' demographic information, medical history, lifestyle measurements, etc., may be recorded as well. Their association with and impact on the outcome variable can then be explored for efficiency gains in testing and estimation of treatment effects. A common approach to adjusting for covariates is to postulate a certain regression model, which gives treatment comparisons conditional on values of the covariates. It is well known that treatment effects may have different interpretations in conditional and unconditional (on covariate value) models. Indeed, except for linear and exponential regression models, the conditional and unconditional approaches generally lead to different parameter values for the treatment effect. We refer to Gail (1984) for a comprehensive discussion on the subject.

Since the unconditional treatment effect is of primary interest here, it is natural for us to avoid any modeling of the relationship between the outcome variable and baseline covariates. Yet it is also desirable that we make best use of the information in the covariates to improve efficiency. To this end, we explore the empirical likelihood methodology to develop a model-free approach to covariate adjustment. We demonstrate that such an approach is natural for nonparametric covariate adjustment and optimal in terms of efficient use of available information.

3. EMPIRICAL LIKELIHOOD BASED METHODS FOR NONPARAMETRIC COVARIATE ADJUSTMENT

Being first implicitly used in Thomas and Grunkemeier (1975), empirical likelihood was developed into a general methodology by Owen (1988, 1990). Given $(Y_i, Z_i, X_i), i = 1, \ldots, n$, assumed to be independent with a common cumulative distribution function (CDF) $F_0$, the empirical likelihood function is a nonparametric likelihood function of the CDF $F$
where \((y_i, z_i, x_i)\) is the observed value of \((Y_i, Z_i, X_i)\), \(p_i = dF(y_i, z_i, x_i) = P(Y_i = y_i, Z_i = z_i, X_i = x_i), i = 1, \ldots, n\). Without additional constraints (other than \(p_i \geq 0\) and \(\sum_{i=1}^{n} p_i = 1\)), it is well known that the empirical distribution function is the nonparametric maximum likelihood estimate of \(F_0\).

This section is devoted to the development of an empirical likelihood based method for nonparametric covariate adjustment arising from a typical randomized clinical trial. Subsection 3.1 develops an empirical likelihood ratio based test and establishes its asymptotic properties. The subsequent subsection deals with the dual problem of estimating treatment effects via maximizing the empirical likelihood with the number of constraints exceeding the number of parameters. Subsection 3.3 extends the results of 3.1 and 3.2 to the situation in which the number of constraints increases with the sample size. Asymptotic normality and Wilks type \(\chi^2\) approximation as well as asymptotic efficiency are established for all the cases under suitable regularity conditions.

3.1 Testing Treatment Differences

Empirical likelihood methodology for inference is based on maximizing the nonparametric likelihood (4) subject to appropriately formulated and problem-specific constraints. For the two-arm randomized clinical trial specified by (2a), the constraints are generated by

(5a) \[ m(\beta; Y, Z) = (1, Z)^T(Y - \beta_1 - \beta_2 Z). \]

For general \(K\) specified by (2b), it becomes

(5b) \[ m(\beta; Y, Z) = (1, 1_{(Z=1)}, \ldots, 1_{(Z=K)})^T(Y - \beta_1 - \beta_2 1_{(Z=1)} - \ldots - \beta_{(K+1)} 1_{(Z=K)}). \]

The zero-mean property of \(m(\beta; Y, Z)\) uniquely determines the value of \(\beta\) and can be used to obtain estimators through the sample-generated estimating equations. The resulting inference involves only the \(Y_i\) and \(Z_i\).
The availability of the baseline covariates $X_i$ should enable us to obtain additional estimating equations, thereby additional constraints. Indeed, Davidian et al. (2005) and Leon et al. (2003) found that the following form gives a general family of estimating equations:

$$\sum_{k=0}^{K} (1(Z=k) - \pi_k) h_k(X),$$

where $h_k$, $k = 0, 1, \ldots, K$ are arbitrary functions. The independence of $Z$ and $X$ guarantees the zero-mean property of the resulting estimating equations.

It is clear now that the number of zero-mean estimating equations as provided by (5) and (6) exceeds the number of parameters which specify the treatment effect. In fact, the number of possible equations that can be generated from (6) can be unlimited when the baseline covariates $X$ are continuous. Suppose we fix the choice of $h_k$ and consider how to make use of them for efficiency improvement. For notational simplicity, we use $g_r(\beta; Y, Z, X)$ to denote an $r$-vector of the resultant estimating equations that include both (5) and (6). Here $r \geq 2$ in the two-sample case and $r \geq K + 1$ for the general $(K + 1)$-sample case.

It is well known that the empirical likelihood approach links together the inference of certain parameters and the available estimating equations to form a constrained optimization problem. With constraints given by $g_r$, it maximizes $L(F)$ in (4) subject to the following constraints:

$$p_i \geq 0, \quad \sum_{i=1}^{n} p_i = 1, \quad \sum_{i=1}^{n} p_i g_r(\beta; Y_i, Z_i, X_i) = 0.$$  

This optimization problem has a unique maximizer provided that 0 is inside the convex hull of $\{g_r(\beta; y_i, z_i, x_i), i = 1, \ldots, n\}$ for a given $\beta$ (Owen 2001). By applying the Lagrange multiplier argument (Lang 1987), we can easily get $p_i = \{n[1 + \hat{\lambda}^T(\beta) g_r(\beta; y_i, z_i, x_i)]\}^{-1}$, where $\hat{\lambda}$, which is a function of $\beta$, is the solution to

$$\frac{1}{n} \sum_{i=1}^{n} \frac{g_r(\beta; y_i, z_i, x_i)}{1 + \hat{\lambda}^T(\beta) g_r(\beta; y_i, z_i, x_i)} = 0.$$  

Therefore, the resulting profile empirical log-likelihood, as a function of $\beta$, takes form

$$l_E(\beta) = \sum_{i=1}^{n} \log \left[ 1 + \hat{\lambda}^T(\beta) g_r(\beta; y_i, z_i, x_i) \right].$$
Theorem 3.1. Let $\beta^T = (\beta_1^T, \beta_2^T)$, where $\beta_1$ and $\beta_2$ are $q_1$- and $q_2$-vectors. Define

$$T_E = 2l_E(\hat{\beta}_{10}, 0) - 2l_E(\hat{\beta}),$$

the logarithmic empirical profile likelihood ratio for testing $H_0: \beta_2 = 0$, where $\hat{\beta}_{10}$ minimizes $l_E(\beta_1, 0)$ with respect to $\beta_1$ and $\hat{\beta}$ minimizes $l_E(\beta)$. Then, under some mild regularity conditions, $T_E$ converges to $\chi^2_{(q_2)}$ in distribution under $H_0$.

Theorem 3.1 is a direct adaptation of Corollary 5 in Qin and Lawless (1994). It enables us to get the $p$-value in testing the null hypothesis of no treatment difference and to invert the test to obtain the confidence limits. A numerical way to find $\hat{\beta}$, and similarly for $\hat{\beta}_{10}$, is to use a two-stage Newton algorithm. We first specify an initial value $\beta^{(0)}$ for $\beta$ and solve (8) to obtain $\hat{\lambda}(\beta^{(0)})$. Next, we fix $\hat{\lambda}(\beta)$ in (9) at $\hat{\lambda}(\beta^{(0)})$ and minimize (9) over $\beta$ to obtain a new value $\beta^{(1)}$. We iterate the process until convergence.

From Qin and Lawless (1994), it follows that the empirical likelihood ratio test incorporating covariate information through constraints $g_r(\beta; Y, Z, X)$ is always more powerful than the one with $m(\beta; Y, Z)$ only. Moreover, the more constraints we put into $g_r$, the more powerful the test becomes. Because the net effect of the empirical likelihood method with more constraints than parameters is an optimal linear combination of the constraints, choice of additional constraints should therefore be made to avoid redundancy. However, it is not necessary to model the relationship between the covariates and the outcome, as is evident from equation (6); this is a very desirable feature with important practical implications.

For a binary outcome variable, if we are interested in using the log-odds ratio, then we can replace (5b) with

$$m(\beta; Y, Z) = (1, 1_{(Z=1)}, \ldots, 1_{(Z=K)})^T[Y - \phi(\beta_1 + \beta_2 1_{(Z=1)} + \ldots + \beta_{(K+1)} 1_{(Z=K)})],$$

where $\phi(\cdot) = \exp(\cdot)/(1 + \exp(\cdot))$ is the logistic function. We can then follow the same steps to construct the empirical likelihood ratio test. As before, the large sample properties given by Theorem 3.1 continue to hold.
3.2 Maximum Empirical Likelihood Estimate of Treatment Effect

Without adjusting for baseline covariates, the number of estimating equations, derived from the score functions, equals the number of parameters. Solving equations $\sum_{i=1}^{n} m(\beta; Y_{i}, Z_{i}) = 0$ gives us the M-estimator for $\beta$, which is known to be consistent and asymptotically normal (Huber 1981). With covariate adjustment, we have additional estimating equations containing auxiliary information through $\Sigma_{r}$. Since the number of all available estimating equations $r$ exceeds the number of parameters $q = q_{1} + q_{2}$, we cannot obtain the estimators simply by finding zeros of those estimating equations. One way to handle overly constrained problem is to form $q$-dimensional linear combinations of all available estimating equations so that the resulting set of equations has a unique solution. One can further evaluate the limiting covariance matrix of the estimator to identify the optimal choice of such linear combinations; cf. Goldambe and Heyde (1987). Because the empirical likelihood method with overly constrained estimating equations can result in the optimal combination (Qin and Lawless 1994), it provides a nature alternative. The following result follows directly from Qin and Lawless (1994).

**Theorem 3.2.** Let $D_{r} = E[\partial g_{r}(\beta_{0})/\partial \beta^{T}]$ and $\Sigma_{r} = E(g_{r}g_{r}^{T})$. Then, under certain regularity conditions, we have

$$n^{1/2}(\hat{\beta} - \beta_{0}) \rightarrow N(0, (D_{r}^{T}\Sigma_{r}^{-1}D_{r})^{-1}),$$

where $\hat{\beta}$ is the maximum empirical likelihood estimate (MELE).

The theorem above allows us to construct Wald-type confidence intervals using the robust variance estimate. From Corollary 2 of Qin and Lawless (1994), it follows that $\hat{\beta}$ has the smallest asymptotic variance among all the $q$-dimensional linear combinations of $g_{r}(\beta; Y, Z, X)$. In particular, when $r = q$, the maximum empirical likelihood estimator $\hat{\beta}$ will be asymptotically equivalent to the M-estimator. Furthermore, Corollary 1 of Qin and Lawless (1994) ensures that the more constraints being put into the optimization problem, the more precision one can achieve.

As an example, consider again a two-arm clinical trial with a binary outcome variable and a continuous covariate $X$, and suppose the log-odds ratio is of interest.
We can incorporate both linear and quadratic terms of $X$ by using constraints
\[
g_r(\beta; Y, Z, X) = \left((1, Z)[Y - \phi(\beta_1 + \beta_2 Z)], (Z - \pi_1), (Z - \pi_1)X, (Z - \pi_1)X^2\right)^T.
\]

The resulting estimator will be more efficient than the M-estimator from $(1, Z)^T[Y - \phi(\beta_1 + \beta_2 Z)]$. Note that, for regression model based covariate adjustment, Robinson and Jewell (1991) demonstrated that including predictive covariates in the logit will always result in a loss of precision. In contrast, for our empirical likelihood approach, including predictive covariates in the constraints will never lead to an increase in the asymptotic variance. The fact that incorporating additional estimating equations always improves efficiency makes the empirical likelihood approach advantageous and convenient.

### 3.3 Empirical Likelihood With Growing Number of Constraints

Since we can achieve more precision by increasing the number of constraints, it is intuitive that semiparametric efficiency may be attained when the number of constraints grows with the sample size. In this connection, we consider in this subsection the empirical likelihood based covariate adjustment when the number of constraints grows to infinity as $n \to \infty$. Note here that the dimension of $\beta$, which is of primary concern, remains fixed.

Suppose besides the $q$-dimensional score $m(\beta; Y, Z)$, the auxiliary information is contained in an $r_n$-vector of estimating equations $g_{r_n}(\beta) = (m^T(\beta; Y, Z), V_n^T)^T$. Instead of a fixed number $r$, $r_n$ here will grow to infinity with $n$ at a certain rate. The $j^{th}$ component of $V_n$ has the form $(1_{Z=k} - \pi_k)h_j(X)$ for $j = 1, \ldots, r_n - q$, where $h_j$ is a real-valued function. The following conditions will be used.

(C1) There exists a non-random $(r_n - q) \times (r_n - q)$ matrix $W_n$ such that (i)-(iii) below are satisfied for $g_{r_n}(\beta) = (m^T(\beta; Y, Z), (W_n V_n)^T)^T$.

(i) Components of $g_{n,i}$, $i = 1, \ldots, n$, are uniformly bounded by a finite constant $M > 0$, where $g_{n,i}(\beta) = g_{r_n}(\beta; Y_i, Z_i, X_i)$.

(ii) Eigenvalues of $\Sigma_{n,g} = E(g_{r_n}(\beta_0)g_{r_n}(\beta_0)^T)$ are bounded away from zero and infinity.
There exists a \( q \times (r_n - q) \) non-random matrix \( A_n \) such that

\[
A_n W_n V_n \to \sum_{k=0}^{K} (1_{Z=k}) - \pi_k) E( m(\beta; Y, Z) | Z = k, X ) \quad \text{in } L^2.
\]

(C2) The growth rate of \( r_n \) is limited to \( r_n^3 = o(n) \).

(C3) Matrix \( \tilde{\Sigma} = E(\tilde{m}\tilde{m}^T) \) is positive definite, where

\[
\tilde{m} = m(\beta; Y, Z) - \sum_{k=0}^{K} (1_{Z=k}) - \pi_k) E( m(\beta; Y, Z) | Z = k, X ).
\]

**Theorem 3.3.** Let \( \hat{\beta}_n \) be the maximum empirical likelihood estimate based on constraints \( g_{r_n}^*(\beta) \) and \( D_m = E(\partial m(\beta_0) / \partial \beta^T) \). Then, under Conditions C1-C3,

\[
n^{1/2}(\hat{\beta}_n - \beta_0) \to N\left( 0, (D_m^T \tilde{\Sigma}^{-1} D_m)^{-1} \right).
\]

Minimizing the asymptotic variance of the M-estimator from the class of arbitrary \( q \)-dimensional unbiased estimating equations, Zhang et al. (2008) derived the semiparametric efficiency bound for the estimators of treatment effect. From Zhang et al. (2008) and Theorem 3.3, we have the following result.

**Corollary 3.4.** The limiting variance-covariance matrix, \( (D_m^T \tilde{\Sigma}^{-1} D_m)^{-1} \), achieves the semiparametric efficiency bound, i.e., \( \hat{\beta}_n \) in Theorem 3.3 is asymptotically efficient.

**Theorem 3.5.** Under Conditions C1-C3,

\[
\| \hat{D}(\hat{\beta}_n) S_n^{-1}(\hat{\beta}_n) \hat{D}(\hat{\beta}_n) - D_m^T \tilde{\Sigma}^{-1} D_m \| = o_p(1).
\]

Throughout, \( \| \cdot \| \) is used to denote the Euclidean norm. Theorem 3.3 states that the listed conditions are sufficient to ensure standard asymptotic properties of the MELE.
Moreover, Corollary 3.4 states that when the number of constraints grows to infinity at a certain rate, the MELE achieves the semiparametric efficiency as derived in Zhang (2008). In Theorem 3.3, \( g_{r_n} \) is essentially a linear transformation of \( g_{r_n}^* \). Since a linear transformation does not change the constraints, the estimator using \( g_{r_n} \) will be the same as that using \( g_{r_n}^* \). The fact that the MELE will not be affected by a linear transformation of the constraints greatly facilitates the applicability of the empirical likelihood approach because we can just throw in all the constraints we have without forming the appropriate combination of them. For example, \( E[g_{r_n}^*(g_{r_n}^*)^T] \) might be ill conditioned but we can still use it as long as there exists a \( W_n \) such that the corresponding \( \Sigma_{n,g} \) is better conditioned. For this reason, we will not distinguish among linear transformations of constraints in the following discussion.

Theorem 3.3 holds for a general \( q \)-dimensional score \( m \) as long as some regularity conditions in the case of fixed number of constraints (Qin and Lawless 1994) are satisfied, including \( E \left( \partial m(\beta; Y, Z)/\partial \beta^T \right) \) is of full rank \( p \), \( \| \partial m(\beta; Y, Z)/\partial \beta^T \| \) and \( \| \partial^2 m(\beta; Y, Z)/\partial \beta \partial \beta^T \| \) can be bounded by some integrable function in a neighborhood of \( \beta_0 \) and \( \partial m(\beta; Y, Z)/\partial \beta \) and \( \partial^2 m(\beta; Y, Z)/\partial \beta \partial \beta^T \) are continuous in this neighborhood.

Condition C2 imposes an upper bound on the growth rate of the number of constraints at which a well-behaved MELE can be obtained. In practice, the number of constraints need not be large. In fact, we find that additional gain by including an extra constraint diminishes quickly, due to the optimal use of constraints by the empirical likelihood method. It is important to note that the asymptotic normality and efficiency are not affected by the choice of \( r_n \), as long as it satisfies C2. It is certainly of theoretical interest to find the sharp upper bound for \( r_n \) to grow such that the resulting estimate is still asymptotically normal and efficient. But we will not get into this complication here since finding the optimal rate is not our main concern. If we knew the conditional expectations in Condition C3, the optimal estimating equations \( \tilde{m} \) would be the constraints that lead to the optimal estimator. Although they are unknown in practice, it is clear that Condition C3 is fairly mild.
For Condition C1, we need to make use of the orthogonality and boundedness of certain basis functions to properly design $h(X)$ in the constraints. Suppose $Z = 0, 1, 2$ and the empirical CDF of the one dimensional auxiliary covariate $X$ is $F_n(x) = n^{-1} \sum_{i=1}^{n} 1_{(X_i \leq x)}$. By making use of multivariate Fourier expansion, the arguments can be generalized to the high dimensional auxiliary covariate case. Let $g^*_n(\beta) = (m^T(\beta; Y, Z), (1 - \pi_1), \hat{s}_{11}, \ldots, \hat{s}_{1d_n}, \hat{c}_{1d_n}, (1 - \pi_2), \hat{s}_{21}, \ldots, \hat{s}_{2d_n}, \hat{c}_{2d_n})^T$, where $1_k = 1_{(Z = k)}$, $r_n = 4d_n + q + 2$, $\hat{s}_{ij} = (1 - \pi_i) \sin(2\pi j F_n(X))$, $\hat{c}_{ij} = (1 - \pi_i) \cos(2\pi j F_n(X))$, $i = 1, 2$, $j = 1, \ldots, d_n$. It can be shown that, when $d_n = o(n^{1/4})$, (i)-(iii) are satisfied. For example, we can apply the fact that those basis functions are orthogonal when their arguments are $U[0, 1]$ and they are bounded to show (i) and (ii) hold. Because the procedure is invariant under linear transformations, the eigenvalues can grow with $n$ if all of them grow at the same rate. However, we do not believe in general they can grow at different rates since the covariance matrix is sandwiched in the variance-covariance expression, which needs to be well-conditioned. Furthermore, (iii) can be verified by taking the expansion of the conditional expectations. Likewise, we may apply other orthogonal basis functions that are bounded. For example, we can use the Legendre polynomials of $(2F_n(X) - 1)$ which are bounded by 1 on $[-1,1]$. Legendre polynomials, i.e. $1, x, (3x^2 - 1)/2, \ldots$, are linear transformations of polynomial terms $1, x, x^2, \ldots$. Therefore we can also use polynomial terms of $(2F_n(X) - 1)$ in the auxiliary constraints due to linear transformation invariance of the empirical likelihood. As pointed out by a referee, the standard independence assumption for empirical likelihood is violated due to the plug-in estimator $F_n$. Intuitively, the validity of using $F_n$ instead of $F$ relies on the fact that those constraints are still zero-mean conditioning on all the covariates. A rigorous proof can be found in the Appendix.

Analogous to the case with a fixed number of constraints, let $l(\beta) = \sum_{i=1}^{n} \log \left( 1 + \tilde{\lambda}_{n,i}(\beta) g_{n,i}(\beta) \right)$. The empirical likelihood ratio statistic for testing $H_0 : \beta = \beta_0$ is

$$T_{1n} = 2l(\beta_0) - 2l(\hat{\beta}_n).$$

Then under Conditions C1-C3, the Wilks type theorem of convergence to the $\chi^2$ distribution is still valid for testing the null hypothesis of no treatment effect.
Theorem 3.6. Suppose that Conditions C1-C3 are satisfied. Then, under the null hypothesis $H_0$, $T_{1n}$ converges in distribution to $\chi^2_{(q)}$ as $n \to \infty$.

More generally, we can test hypothesis on a subset of treatment effects $\beta$ instead of all components of it. For instance, we may be interested in testing whether $\beta_2 = 0$ in the simple example (2a). Specifically, let $\beta^T = (\beta_1^T, \beta_2^T)^T$, where $\beta_1$ and $\beta_2$ are $q_1$- and $q_2$-vectors, respectively. For $\widetilde{H}_0 : \beta_1 = \beta_{10}$, the profile empirical likelihood ratio test statistic is simply

$$T_{2n} = 2l(\beta_{10}, \hat{\beta}_{20}) - 2l(\hat{\beta}_n),$$

where $\hat{\beta}_{20}$ minimizes $l(\beta_{10}, \beta_2)$ with respect to $\beta_2$. The following result shows that a Wilks type $\chi^2$ approximation still holds.

Corollary 3.7. Suppose that Conditions C1-C3 are satisfied. Then, under the null hypothesis, $T_{2n}$ converges in distribution to $\chi^2_{(q_1)}$ as $n \to \infty$.

Auxiliary information can be used to not only increase the precision of estimated treatment effects, but to also increase power in hypothesis testing. To evaluate power, we need to derive the asymptotic distribution of the test statistic under the alternative hypothesis. We shall consider the contiguous alternative which deviates from the null by the order of $O(n^{-1/2})$; cf. Hajek, Sidak and Sen (1999) and Serfling (1980). For notational convenience, let $A = D_m^T \tilde{\Sigma}^{-1} D_m$ and write

$$A = \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix},$$

where $A_{ij} = E(\partial m^T(\beta_0)/\partial \beta_i) \tilde{\Sigma}^{-1} E(\partial m(\beta_0)/\partial \beta_j^T)$, $i = 1, 2$ and $j = 1, 2$.

Theorem 3.8. Suppose that Conditions C1-C3 are satisfied. Then under the sequence of contiguous alternatives $H_a : \beta = \beta_a = \beta_0 + h/\sqrt{n}$, the empirical likelihood ratio test statistic $T_{1n}$ converges in distribution to a noncentral $\chi^2$ with degrees of freedom $q$ and noncentrality parameter $h^T A h$.

Similarly, the noncentrality parameter of the limiting $\chi^2$ distribution becomes the projected Fisher information when there are nuisance parameters.
Corollary 3.9. Under the same assumptions as those in Theorem 3.8 and with $H_a$ replaced by $\tilde{H}_a : \beta_1 = \beta_{1a} = \beta_{10} + h_1/\sqrt{n}$, the empirical likelihood ratio test statistic $T_{2n}$ in (14) converges in distribution to a noncentral $\chi^2$ with degrees of freedom $q_1$ and noncentrality parameter $h_1^T(A_{11} - A_{12}A_{22}^{-1}A_{21})h_1$.

It can be seen that the empirical likelihood approach reproduces the standard asymptotic results in parametric likelihood theory (Cox and Hinkley 1974). Similar to the estimation problem, adding more constraints will result in more powerful tests. When the number of constraints goes to infinity, the corresponding tests become asymptotically most powerful.

4. NUMERICAL STUDIES

In this section, we discuss computational issues arising from implementing the constrained optimization problems and report simulation results associated with the empirical likelihood based covariate adjustment method.

The primary step in computing the empirical likelihood is to maximize (4) subject to constraints (11). The lagrangian is

$$P_*(p, \beta, \lambda, \gamma) = \sum_{i=1}^{n} \log_*(p_i) + n\lambda^T \sum_{i=1}^{n} p_i g_i(\beta; y_i, z_i, x_i) + n\gamma(\sum_{i=1}^{n} p_i - 1),$$

where $\lambda$ and $\gamma$ are the Lagrange multipliers and $\log_*$ is a modified natural logarithm defined in Owen (2001). Thus, we obtain estimators for $p$ and $\beta$ by differentiating $P_*$ with respect to $p$, $\beta$, $\lambda$ and $\gamma$ and setting them to 0.

Working directly with $n + q + r + 1$ free variables involves gradient and Hessian matrices of daunting dimensions. Alternatively we may use the two-stage Newton algorithm as discussed in Section 3.1 that can eliminate some parameters. Nonetheless, unlike the usual testing case where $\beta$ is fixed at $\beta_0$, the outer stage in the two-stage Newton algorithm, i.e. minimization over $\beta$ while keeping $\lambda$ fixed, is difficult in practice because of the possibility of a non-positive definite Hessian matrix. Zedlewski (2008) points out that “Concentrating out some parameters leads
to a smaller optimization problem, but it can make it more difficult. Thus the two-stage Newton algorithm is fast but unreliable and can lead to frustrating convergence problems. In most cases $n$ is much greater than $q + r$, so the largest block of the Hessian is an $n \times n$ diagonal matrix.”. In our implementation, we use a Matlab package “matElke”, which solves the primal problem by including modern optimization codes exploiting matrix sparsity. We find the package to be both robust and fast. The link to the Matlab package and the code to implement our method can be found at [http://www.stat.columbia.edu/~xwu/software.html](http://www.stat.columbia.edu/~xwu/software.html).

4.1 Estimation

The simulation results reported below are all based on 5000 Monte Carlo replications. The sample size is chosen to be 200 throughout. We consider the case of two treatment groups with the treatment indicator $Z$ generated with $P(Z = 0) = P(Z = 1) = 0.5$. The response variable $Y$ is binary with logit \( \{E(Y|Z)\} = \beta_1 + \beta_2 Z \). The parameter of interest is either $\beta = (\beta_1, \beta_2)^T$ or $\beta_2$.

In the first scenario, the auxiliary covariate $X$ is generated as a one dimensional Normal random variable with mean 0 and different variances. The magnitude of the variance correlates with the influence of $X$ on the response. Given $Z$ and $X$, $Y$ is then generated as Bernoulli according to logit \( \{P(Y = 1|Z = g, X)\} = \alpha_0 g + \alpha_g X \), where $\alpha_{00} = 0.3$, $\alpha_{01} = 1$, $\alpha_0 = 1$, $\alpha_1 = 1.5$ and $g = 0$ or 1.

From Table 1 we see that when the standard deviation of $X$ is 2, the Monte Carlo standard errors gradually decrease and approach the optimal ones. From “marginal” to “5 Fourier”, the standard errors drop significantly. However, additional constraints beyond “5 Fourier” do not appear to have much impact on further variance reduction. Note that a large number of additional constraints require substantially more computing time. Thus, we will only compare the results of “marginal” with “5 Fourier” in the other cases. A single (i.e., nonparallel) process that calculates the maximum empirical likelihood estimate and the p-value for testing the null hypothesis of no treatment difference takes, on average, less that 2 seconds to run for a data set of
200 samples using 5 constraints. The computation time is estimated using a 2.33GHz processor on a server with 8GB RAM.

Table II also shows that the means of Monte Carlo estimates differ from the true value of $\beta$ at the third decimal place and the coverage probabilities are around 0.95. The Monte Carlo standard errors of estimates from five estimating equations are generally smaller than those from marginal models. The improvement becomes more pronounced when the variance of X becomes larger. Also, the average length of 95% Wald confidence intervals are smaller than those of marginal models.

In the second scenario, the link function is quadratic in $X$, i.e., $\logit\{P(Y = 1 | Z = g, X)\} = \alpha_0 + \alpha_g X^2$, with the same $\alpha_0$ and $\alpha_g$ values, $g = 0, 1$. From Table II, we see that the coverage probabilities are satisfactory and close to their nominal levels as in the first scenario. The biases are slightly larger, however, they are still small relative to the standard errors. As expected, the Monte Carlo standard errors and the average lengths of 95% Wald confidence intervals from five estimating equations are smaller than those from the two marginal ones.

In the third scenario, there are two auxiliary covariates $X_1$ and $X_2$ and the response $Y$ is generated as $\logit\{P(Y = 1 | Z = g, \mathbf{X})\} = \alpha_{00} + \alpha_{0g} X_1 + \alpha_{1g} X_2$, $g=0,1$, with $\alpha_{00} = 0.3, \alpha_{01} = 1, \alpha_{10} = 1, \alpha_{11} = 1.5, \alpha_{20} = 2, \alpha_{21} = 1.5$. The estimating equations for the marginal method remain the same since there is no covariate adjustment involved. Let $\kappa(Z) = \sqrt{2}(2Z - 1)$ and $W_k = 2\pi F_{\kappa}(X_k), k = 1, 2$. The empirical likelihood method with constraints, $\kappa(Z), \kappa(Z)\sin(W_1), \kappa(Z)\cos(W_1), \kappa(Z)\sin(W_2), \kappa(Z)\cos(W_2)$, except the marginal estimating equations is denoted by “7 Fourier”. From Table III, the performance of the estimates is similar to the previous two scenarios.

4.2 Testing

With the same data generating process as in the preceding subsection, the corresponding hypothesis testing results are presented in Tables IV, V and VI. In each scenario, the profile empirical likelihood ratio test is used to test the null hypothesis $\tilde{H}_0 : \beta_2 = 0$. CovProb denotes coverage probabilities for testing $\beta_2 = \beta_{20}$. We have
the following observations. First, in all three tables, both coverage probabilities of the profile empirical likelihood ratio tests are close to the nominal 95% level. Second, the attained power from 5 estimating equations is larger than that from marginal estimating equations. Third, when $X$ is one dimensional, the gain in power is more significant as the standard deviation of $X$ increases.

5. APPLICATION

We apply the proposed empirical likelihood based approach to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-I trial data, which were kindly provided to us by Karen Pieper from the Duke Clinical research Institute. The primary endpoint was 30-day death, which occurred in 6.29% of 10366 patients randomly assigned to tissue plasminogen activator (TPA) ($g=1$), 7.32% of 10354 patients randomly assigned to skreptokinase (SK) with IV heparin ($g=2$), 6.99% of 10303 patients randomly assigned to a combination of SK and TPA ($g=3$) and 7.24% of 9773 patients randomly assigned to SK with SQ heparin ($g=4$). Besides treatment assignment and outcome, some baseline auxiliary covariates concerning demographics (age, sex, weight, height), risk factors (hypertension, diabetes, smoking, hypercholesterolemia), other history (family history of MI, previous MI, previous angina, previous revascularization) and presenting characteristics (blood pressure, tachycardia, anterior infarct location, killip class, ST elevation on electrocardiography) were recorded on each subject. In Steyerberg et al. (2000), the relative prognostic strength of 17 baseline covariates was evaluated by their univariate $\chi^2$ model, which was calculated as the difference in -2 log-likelihood between a univariate logistic regression model with and without the characteristic. The strongest prognostic factor was age and this was further confirmed by the $R^2$ measure on the log-likelihood scale, which approximately indicated the percentage of variance explained. Except for the calculation of correlation, adjustment for important predictors such as age is always recommended in the case of short-term death after acute myocardial infarction. Thus, we will compare unadjusted and age-adjusted results for the four treatment groups.
The marginal model between the 30-day death (Y) and treatment assignment (Z) is given by logit\{E(Y|Z)\} = \beta_1 + \beta_21_{(Z=2)} + \beta_31_{(Z=3)} + \beta_41_{(Z=4)}. For the age(X) adjustment, we use 9 auxiliary constraints \((1_{(Z=g)}-0.25), (1_{(Z=g)}-0.25)F_n(x)\) and \((1_{(Z=g)}-0.25)F_{2n}(x), g = 2, 3, 4\), where \(F_n(x)\) is the empirical c.d.f. of age.

The unadjusted estimates \((\hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3, \hat{\beta}_4)\) are (-2.7014, 0.1630, 0.1129, 0.1517) with standard errors (0.04109, 0.05619, 0.05670, 0.05557). Estimates adjusted for age are (-2.7014, 0.1628, 0.1126, 0.1521) with standard errors (0.04109, 0.05619, 0.05670, 0.05556). The p-values for the unadjusted and adjusted hypothesis testing of \(\beta_2 = \beta_3 = \beta_4 = 0\) are 0.0136 and 0.0135, respectively.

The unadjusted test is already significant, so the additional improvement in p-value after covariate adjustment only reconfirms the scientific conclusion. However, if the sample size were smaller, the change in p-value might be more consequential. For illustrative purposes, we randomly draw a subsample of size 20000 from the complete data and pretend that is what we had in reality. In one of these cases, the p-values for the unadjusted test of \(\beta_2 = \beta_3 = \beta_4 = 0\) is 0.0391 while it becomes 0.0362 after adjusting for age. In another case, it changes from 0.0508 to 0.0458.

6. DISCUSSION

Nonparametric covariate adjustment is of importance in analysis of randomized clinical trial data. When properly done, it can result in efficiency improvement while maintaining the nonparametric nature of the usual tests. Empirical likelihood approach is nonparametric, constraint based and efficient in extracting information from data.

For randomized clinical trials, covariate information with no model assumption can be extracted from certain type of constraints or estimating equations. We propose an empirical likelihood based approach for covariate adjustment. The resulting likelihood ratio test is shown to have the usual Wilks type \(\chi^2\) approximation, with increased power as the number of constraints increases. The corresponding maximum empirical likelihood estimate also enjoys similar asymptotic properties. We
demonstrate that the $\chi^2$ and normal approximations continue to hold as the number of constraints grows with sample size. We further show that in doing so the semiparametric efficiency can be achieved.

One of the practical issues is how to select basis functions in the constraints. From our experiences with simulations and real data analysis, it appears that there is no universal way to deal with this issue. A related issue is how many basis functions should be used. One ad hoc way to do that is to consider variance reduction when additional constraints are added. We believe that if initial basis functions are properly chosen, then only a very small number of constraints will be needed.

It will be of interest to extend this empirical likelihood based nonparametric covariate adjustment to other situations, including observational studies. Of particular importance are the survival and longitudinal studies where the response variables may be dependent or causal. For survival data, Lu and Tsiatis (2008) have introduced a general model framework for covariate adjustment and derived a semiparametric efficient score. We believe a similar approach, which makes use of suitable covariate based constraints and achieves the asymptotic efficiency, can be developed.

**APPENDIX**

Here we provide proofs of the theoretical results presented in the previous sections.

For notational convenience, let $G_n(\beta) = \max_{1 \leq i \leq n} \|g_{n,i}(\beta)\|$, $\Sigma_{n,m} = E(m_{rn}(\beta_0)m_{rn}^T(\beta_0))$, $\Sigma_{n,\text{opt}} = E(m_{rn}^{\text{opt}}(\beta_0)(m_{rn}^{\text{opt}}(\beta_0))^T)$, $D_{rn} = E(\partial g_{rn}(\beta_0)/\partial \beta^T)$, $D_{mn} = E(\partial m_{rn}(\beta_0)/\partial \beta^T)$, and $D_{\text{opt}} = E(\partial m_{rn}^{\text{opt}}(\beta_0)/\partial \beta^T)$.

**Lemma 1.** The probability that zero is outside the convex hull spanned by $\{g_{n,i}, i = 1, \ldots, n\}$ goes to zero as $n \to \infty$.

**Proof.** This follows from Lemma 4.2 in Hjort et al. (2009) and discussions thereof.

**Lemma 2.** Under (i), (ii) and C2, the eigenvalues of $S_n(\beta_0)$ are bounded away from 0 and $\infty$. 

□
Proof. It can be shown by making use of proofs of condition (D4) and Lemma 4.5 in Hjort et al. (2009).

Lemma 3. Under (i),(ii) and C2,

\[ \left\Vert \hat{\chi}_n(\beta_0) \right\Vert = O_p(n^{-1/2}r_1^{1/2}) \]

\[ \sup_{\left\Vert \beta - \beta_0 \right\Vert \leq n^{-1/3}} \left\Vert \hat{\chi}_n(\beta) \right\Vert = O_p(n^{-1/3}) \]

\[ \sup_{\left\Vert \beta - \beta_0 \right\Vert \leq n^{-1/3}} \left\Vert \hat{\chi}_n(\beta) - S_n(\beta)^{-1} \bar{g}_n(\beta) \right\Vert = O_p(n^{-2/3}r_1^{1/2}) \]

Proof. Under (i),(ii) and C2, we can apply results in Portnoy (1988) to get

\[ \left\Vert n^{1/2} \bar{g}_n(\beta_0) \right\Vert = O_p(r_1^{1/2}) \]

Under (i),

\[ G_n(\beta) \leq Mr_1^{1/2} = O_p(r_1^{1/2}) \]

Write \( \hat{\chi}_n(\beta) = \left\Vert \hat{\chi}_n(\beta) \right\Vert u_n(\beta) \), where \( \left\Vert u_n(\beta) \right\Vert = 1 \). Then similar to (8), we can show that

\[ 0 = u_n^T(\beta) \frac{1}{n} \sum_{i=1}^{n} \frac{g_{n,i}(\beta)}{1 + \hat{\chi}_n^2(\beta)g_{n,i}(\beta)} \leq u_n^T(\beta) \bar{g}_n(\beta) - \frac{\left\Vert \hat{\chi}_n(\beta) \right\Vert}{1 + \left\Vert \hat{\chi}_n(\beta) \right\Vert G_n(\beta)} \text{mineig}(S_n(\beta)), \]

where \( \text{mineig}(M) \) stands for the minimum eigenvalue of the matrix \( M \). Therefore, we have

\[ \left\Vert \hat{\chi}_n(\beta) \right\Vert \left( \text{mineig}(S_n(\beta)) - u_n^T(\beta) \bar{g}_n(\beta) G_n(\beta) \right) \leq u_n^T(\beta) \bar{g}_n(\beta), \]

from which we know that (13) holds due to (18), (19) and Lemma 2.

When \( \left\Vert \beta - \beta_0 \right\Vert \leq n^{-1/3} \), define

\[ L_n = \max_{j,k} |S_{n,j,k}(\beta) - S_{n,j,k}(\beta_0)|. \]

Using the same technique as in Lemma 2, \( r_nL_n = o_p(1) \) ensures that the minimum eigenvalue of \( S_n(\beta) \) is bounded away from zero. Since there are only finitely many terms in \( g_{r_n} \) containing \( \beta \), due to the \( \delta \)-method, this can be further reduced to
∥β − β_0∥ = o(r_n^{-1}), which is true under C2. By expanding \( \overline{g}_n(β) \) in the \( n^{-1/3} \) neighborhood of \( β_0 \), we obtain \( \overline{g}_n(β) = O_p(n^{-1/3}) \) uniformly in \( ∥β − β_0∥ ≤ n^{-1/3} \). Then (16) follows from equation (20).

We know that \( \hat{λ}_n(β) \) satisfies the constraint \( n^{-1} \sum_{i=1}^n g_{n,i}(β) / \{1 + \hat{λ}_n^T(β) g_{n,i}(β)\} = 0 \), which implies (22)

\[
\hat{λ}_n(β) = S_n(β)^{-1} \overline{g}_n(β) + S_n(β)^{-1} \frac{1}{n} \sum_{i=1}^n g_{n,i}(β) \frac{u_n^T(β) g_{n,i}(β) g_{n,i}^T(β) u_n(β)}{1 + \hat{λ}_n(β) g_{n,i}(β)} \left\| \hat{λ}_n(β) \right\|^2.
\]

By the triangle inequality and some simple algebra, the final term in (22) is bounded by \( O_p(n^{-2/3} r_n^{1/2}) \). Since \( ∥S_n(β)^{-1}∥ = O_p(1) \), (17) follows from (22).

**Lemma 4.** Under Conditions C1-C3,

\[
\left\| D_{n,g}^T Σ_{n,g}^{-1} D_{n,g} − D_{m}^T Σ_{m}^{-1} D_{m} \right\| = o(1).
\]

Proof. Let \( m_{r_n} = m(β; Y, Z) + A_n W_n V_n \). Since \( A_n W_n V_n \) does not involve \( β \), we have

(23)

\[
D_{m,n}^T Σ_{n,m}^{-1} D_{m,n} = D_{m}^T Σ_{m}^{-1} D_{m},
\]

which by (iii), converges to \( D_{m}^T Σ_{m}^{-1} D_{m} \).

Second, following Qin and Lawless (1994), for any \( n \), we have

\[
D_{r_n}^T Σ_{n,r_n}^{-1} D_{r_n} = D_{opt,n}^T Σ_{n,opt}^{-1} D_{opt},
\]

where \( m_{r_n}^{opt} = A_{opt}(β) g_{r_n} \) is a \( q \)-vector and \( A_{opt}(β) \) is the optimal linear combination of \( g_{r_n} \). So it suffices to show the following difference is zero:

(24)

\[
D_{opt}^T Σ_{n,opt}^{-1} D_{opt} − D_{m}^T Σ_{m}^{-1} D_{m}.
\]

Given (23), (24) is positive definite due to optimality. Furthermore,

\[
D_{opt}^T Σ_{n,opt}^{-1} D_{opt} − D_{m}^T Σ_{m}^{-1} D_{m} = D_{opt}^T Σ_{n,opt}^{-1} D_{opt} − D_{m}^T Σ_{m}^{-1} D_{m} + D_{m}^T Σ_{m}^{-1} D_{m} − D_{m}^T Σ_{m}^{-1} D_{m}.
\]
By Zhang et al. (2008), we know that $D_m^T \tilde{\Sigma}^{-1} D_m$ is the semiparametric efficiency bound, which implies the first difference is non-positive definite. Since the second difference is $o_p(1)$, we know (24) is nonpositive definite. □

**Lemma 5.** Under (i), (ii) and C2, $\|\hat{\beta}_n - \beta_0\| < n^{-1/3}$.

Proof. We first consider $\beta$ on the $n^{-1/3}$ sphere of $\beta_0$, i.e. $\beta - \beta_0 = un^{-1/3}$, where $u$ is a unit vector. On the one hand, by the Taylor series expansion and Lemma 3

$$2 \sum_{i=1}^n \log \left(1 + \tilde{\lambda}_n^T (\beta) g_{n,i}(\beta)\right) = 2n \tilde{\lambda}_n^T (\beta) \tilde{\Sigma}^{-1} n^{-1/2} + O_p(n^{-1/3}).$$

By (17), it is equivalent to $n \tilde{\Sigma}^{-1} n^{-1/2} + O_p(n^{-1/3})$. By taking the Taylor series expansion at $\beta_0$, it equals to

$$u^T D_r^T \Sigma_{n,g}^{-1} D_r u n^{1/3} + o_p(n^{1/3}),$$

which is bounded below by $O_p(n^{1/3})$ by Lemma 4. On the other hand, $2 \sum_{i=1}^n \log \left(1 + \tilde{\lambda}_n^T (\beta_0) g_{n,i}(\beta_0)\right) = O_p(n_r)$, which is strictly less than $O_p(n^{1/3})$ by condition C2. Therefore, $\|\hat{\beta}_n - \beta_0\| < n^{-1/3}$. □

**Lemma 6.** Under conditions C1-C3, we have the asymptotic normality of the “influence function”

$$D_{r_n}^T \Sigma_{n,g}^{-1} n^{1/2} \bar{g}(\beta_0) \to N(0, D_m^T \tilde{\Sigma}^{-1} D_m).$$

Proof. We can reduce the problem to the unidimensional case by noting that it suffices to show that for any $q \times 1$ vector $t$,

$$t^T D_{r_n}^T \Sigma_{n,g}^{-1} n^{1/2} \bar{g}(\beta_0) \to N(0, t^T D_m^T \tilde{\Sigma}^{-1} D_m t).$$

First, the variance of the left hand side of (25) is $t^T D_{r_n}^T \Sigma_{n,g}^{-1} D_{r_n} t$, which converges to $t^T D_m \tilde{\Sigma}^{-1} D_m t$ by Lemma 4.
Second, we verify the Lindeberg condition (Billingsley 1986)

\[
\sum_{i=1}^{n} E \left\{ \left[ n^{-1/2} t^T D_{rn}^{-1} g_{n,i}(\beta_0) \right]^2 \mathbf{1} \left[ n^{-1/2} t^T D_{rn}^{-1} g_{n,i}(\beta_0) > \varepsilon \right] \right\}
\]

\[
= E \left\{ \left[ t^T D_{rn}^{-1} g_{rn}(\beta_0) \right]^2 \mathbf{1} \left[ t^T D_{rn}^{-1} g_{rn}(\beta_0) > n^{1/2} \varepsilon \right] \right\} \to 0,
\]

where the last step comes from

\[
P \left( \left| t^T D_{rn}^{-1} g_{rn}(\beta_0) \right| > n^{1/2} \varepsilon \right) \leq E \left( t^T D_{rn}^{-1} g_{rn}(\beta_0) \right)^2 / n \varepsilon^2,
\]

which goes to 0 since the numerator is asymptotically bounded. Hence Lemma 6 holds by the Lindeberg-Feller Central Limit Theorem.

Proof of Theorem 3.3. Let

\[
U_n(\beta, \lambda) = \frac{1}{n} \sum_{i=1}^{n} \frac{g_{n,i}(\beta)}{1 + \lambda^T \partial g_{n,i}(\beta) / \partial \beta} \quad \text{and} \quad V_n(\beta, \lambda) = \frac{1}{n} \sum_{i=1}^{n} \frac{\lambda g_{n,i}(\beta)}{1 + \lambda^T \partial g_{n,i}(\beta) / \partial \beta}.
\]

We know that \((\hat{\beta}_n, \hat{\lambda}_n)\) satisfies

\[
0 = U_n(\hat{\beta}_n, \hat{\lambda}_n)
\]

\[
= \overline{g}_n(\beta_0) + D(\beta_0) (\hat{\beta}_n - \beta_0) - S_n(\beta_0) \hat{\lambda}_n + O_p(n^{-2/3}) \sqrt{r_n}, \quad \text{and}
\]

\[
0 = V_n(\hat{\beta}_n, \hat{\lambda}_n)
\]

\[
= D^T(\beta_0) \hat{\lambda}_n + O_p(n^{-2/3}).
\]

Solving (26) and (27) for \(\hat{\beta}_n - \beta_0\), we get,

\[
n^{1/2} (\hat{\beta}_n - \beta_0) = -n^{1/2} (D(\beta_0)^T S_n^{-1}(\beta_0) D(\beta_0))^{-1} D(\beta_0) S_n^{-1}(\beta_0) \overline{g}_n(\beta_0) + o_p(1).
\]

By triangular inequality and Lemma 4, we can show that

\[
\left\| (D(\beta_0)^T S_n^{-1}(\beta_0) D(\beta_0))^{-1} - (D_m^T \tilde{\Sigma}^{-1} D_m)^{-1} \right\| = o_p(1).
\]
Then Theorem 3.3 follows from (28), (29) and Slutsky’s Theorem.

Proof of Theorem 3.5. Since there are only finitely many terms in $\mathcal{g}_n$ and $S_n$ that contain $\beta$, by the $\delta$-method, we have

$$\left\|\left(\hat{D}^T(\hat{\beta}_n)S_n^{-1}(\hat{\beta}_n)\hat{D}(\hat{\beta}_n)\right)^{-1} - \left(\hat{D}^T(\beta_0)S_n^{-1}(\beta_0)\hat{D}(\beta_0)\right)^{-1}\right\| = o_p(1).$$

Then the result follows from (29).

Proof of Theorem 3.6. Taking the Taylor series expansion, we get

$$T_{1n} = n^{1/2}(\hat{\beta}_n - \beta_0)^T \left[\frac{\partial^2}{\partial \beta \partial \beta^T} \frac{1}{n} \sum_{i=1}^{n} \log \left(1 + \hat{\lambda}_n^T(\beta_0)g_{n,i}(\beta_0)\right)\right] n^{1/2}(\hat{\beta}_n - \beta_0) + o_p(1)$$

$$= n^{1/2}(\hat{\beta}_n - \beta_0)^T A n^{1/2}(\hat{\beta}_n - \beta_0) + o_p(1).$$

Then Theorem 3.3 implies $T_{1n} \rightarrow \chi^2_q$ as $n \rightarrow \infty$, when $H_0$ is true.

Proof of Corollary 3.7. When only $\beta_1$ is specified in the null hypothesis, we write the likelihood ratio statistic as the sum of two differences, each of which can be expanded in a manner similar to that in Theorem 3.6 and we have

$$T_{2n} = \left[2 \sum_{i=1}^{n} \log \left(1 + \hat{\lambda}_n^T(\beta_0)g_{n,i}(\beta_0)\right) + 2 \sum_{i=1}^{n} \log \left(1 + \hat{\lambda}_n^T(\hat{\beta}_n)g_{n,i}(\hat{\beta}_n)\right)\right]$$

$$- \left[2 \sum_{i=1}^{n} \log \left(1 + \hat{\lambda}_n^T(\beta_0)g_{n,i}(\beta_0)\right) + 2 \sum_{i=1}^{n} \log \left(1 + \hat{\lambda}_n^T(\beta_1,\hat{\beta}_2)g_{n,i}(\beta_1,\hat{\beta}_2)\right)\right]$$

$$= n^{1/2}(\beta_{10} - \hat{\beta}_{1n})^T (A_{11} - A_{12}A_{22}^{-1}A_{21}) n^{1/2}(\beta_{10} - \hat{\beta}_{1n}) + o_p(1).$$

The last equation comes from $\hat{\beta}_{20} - \beta_{20} = \hat{\beta}_{2n} - \beta_{20} + A_{22}^{-1}A_{21}(\hat{\beta}_{1n} - \beta_{10}) + o_p(1)$. Thus Corollary 3.7 holds because $n^{1/2}(\hat{\beta}_{1n} - \beta_{10})$ converges in distribution to $N(0, (A_{11} - \ldots$
Proof of Theorem 3.8. Following the same steps as in the proof of Theorem 3.3, we can show that
\[ n^{1/2} A^{-1/2} (\hat{\beta}_n - \beta_0) \rightarrow N(A^{-1/2} h, I). \]
Taking the Taylor series expansion of the empirical likelihood ratio test statistic at \( \beta_0 \), we have
\[ T_1n = n^{1/2} (\hat{\beta}_n - \beta_a + h/\sqrt{n})^T A(\beta_0) n^{1/2} (\hat{\beta}_n - \beta_a + h/\sqrt{n}) + o_p(1), \]
where the second equality comes from \( \beta_a = \beta_0 + h/\sqrt{n} \) being a sequence of contiguous alternatives. Therefore, \( T_1n \rightarrow \chi^2 \) with noncentrality parameter \( h^T A h \) as \( n \rightarrow \infty \) under the alternative \( H_a : \beta = \beta_a = \beta_0 + h/\sqrt{n}. \)

Proof of Corollary 3.9. Similar to the preceding proof, we have under the contiguous alternative
\[ T_2n = n^{1/2} (\beta_{10} - \hat{\beta}_{1n})^T (A_{11} - A_{12} A_{22}^{-1} A_{21}) n^{1/2} (\beta_{10} - \hat{\beta}_{1n}) + o_p(1). \]

In the following part of the APPENDIX, we verify that \( g_{r_n} \) in the examples following Corollary 3.4 satisfies Condition C1. The other conditions are satisfied trivially. Since the Fourier basis are naturally bounded by 1, the uniform boundedness reduces to the boundedness of \( m \) which is of finite dimension and usually holds easily. So (i) is satisfied. Let
\[ V_n = ((1 - \pi_1)/\pi_1, s_{11}, c_{11}, \ldots, s_{1d_n}, c_{1d_n}, (1 - \pi_2)/\pi_2, s_{21}, c_{21}, \ldots, s_{2d_n}, c_{2d_n})^T \]
and $g_{r_n}(\beta) = (m^T(\beta; Y, Z), V_n^T)^T$, where $1_k = 1_{(Z=k)}$, $s_{ij} = \sqrt{2}(1_i - \pi_i) \sin(2\pi j F(X))/\pi_i$, $c_{ij} = \sqrt{2}(1_i - \pi_i) \cos(2\pi j F(X))/\pi_i$, $i = 1, 2, j = 1, \ldots, d_n$. For notation simplicity, we omit $W_n$ in $W_n V_n$ when there is no ambiguity. Then letting $I_d$ denote the $d \times d$ identity matrix, we have the following matrix partition

$$
\Sigma_{n,g} = \begin{bmatrix}
E(mm^T) & E(mV_n^T) \\
E(V_n m^T) & -I_{2dn+1}
\end{bmatrix}.
$$

Thus, by some simple algebra and C3, we can show that the eigenvalues of $\Sigma_{n,g}$ are bounded away from 0 and $\infty$. However, since $F$ is unknown in practice, we typically use $F_n(x) = n^{-1} \sum_{i=1}^n 1\{X_i \leq x\}$ instead. Let

$$
\hat{V}_n(z, x) = ((1 - \pi_1)/\pi_1, \hat{s}_{11}, \hat{s}_{12}, \ldots, \hat{s}_{1d_n}, \hat{c}_{1d_n}, (1 - \pi_2)/\pi_2, \hat{s}_{21}, \hat{c}_{21}, \ldots, \hat{s}_{2d_n}, \hat{c}_{2d_n})
$$

and $\hat{g}_{r_n}(\beta) = (m^T(\beta; Y, Z), \hat{V}_n^T(Z, X))^T$, where $\hat{s}_{ij} = \sqrt{2}(1_i - \pi_i) \sin(2\pi j F_n(x))/\pi_i$, $\hat{c}_{ij} = \sqrt{2}(1_i - \pi_i) \cos(2\pi j F_n(x))/\pi_i$, $i = 1, 2, j = 1, \ldots, d_n$. Define $\varepsilon_n = \hat{g}_{r_n} \hat{g}_{r_n}^T - g_{r_n}g_{r_n}^T$. Then

$$
r_{n,\max} \mid \varepsilon_{n,j,k} \mid \leq 2M^2 r_n \mid \sin \pi d_n (F_n(X) - F(X)) \mid = O_p(r_n^2 n^{-1/2}).
$$

Following the argument in Lemma \[2\] when we let $r_n = o(n^{1/2})$, we know the eigenvalues of $E(\hat{g}_{r_n}(\beta_0) \hat{g}_{r_n}(\beta_0)^T)$ are also bounded away from zero and infinity. So (ii) holds.

Moreover, let $f(z, x) = \sum_{k=0}^K (1_k - \pi_k)E(m(\beta; Y, Z)|Z = k, x)$ and $A_n$ be the Fourier coefficients in the Fourier expansion of $f(z, x)$ with the Fourier basis specified in $\hat{V}_n(z, x)$. We know from Fourier approximation theory that $A_n \hat{V}_n(z, x) \to f(z, x)$ uniformly. Thus, by Condition C3 and the Dominated Convergence Theorem, (iii) is satisfied.

Proof of the validity of the plug-in estimator $F_n$. Checking the derivation of all the theorems, we find that the following two conditions will guarantee the validity of the
theorems when \( F \) is replaced by \( F_n \)

\[
\left\|n^{-1/2} \sum_{i=1}^{n} (\hat{g}_{n,i} - g_{n,i})\right\| = o_p(1)
\]

(30)

\[
\left\|n^{-1} \sum_{i=1}^{n} \left\{ \hat{g}_{n,i} \hat{g}_{n,i}^T - g_{n,i} g_{n,i}^T \right\} \right\| = o_p(1),
\]

(31)

where \( g_{n,i} \) and \( \hat{g}_{n,i} \) are \( g_{r_n} \) and \( \hat{g}_{r_n} \) evaluated at the \( i^{th} \) sample. The norm of a matrix \( M \) is defined to be \( \sup_{u} \|Mu\| \), where \( u \) is a unit vector. The sufficiency of the above two conditions when the number of constraints is fixed can be seen from the existing literature (see, for example, Hjort et al. (2009)).

Denote the \( j^{th} \) component of a vector \( g \) by \( g_j \). Then, for any \( j \), we have

\[
E \left\{ \left( n^{-1/2} \sum_{i=1}^{n} (\hat{g}_{n,i}^j - g_{n,i}^j) \right)^2 \left| X_1, \ldots, X_n \right. \right\} \leq C_1 r_n^2 \|F_n - F\|_\infty^2,
\]

where \( C_1 \) is a universal constant. Therefore,

\[
E \left\{ \left\|n^{-1/2} \sum_{i=1}^{n} (\hat{g}_{n,i} - g_{n,i}) \right\|^2 \left| X_1, \ldots, X_n \right. \right\} \leq C_1 r_n^2 \|F_n - F\|_\infty^2 = O_p(r_n^3/n),
\]

which converges to 0 in probability due to C2. By Chebyshev’s inequality, we know that for any \( \varepsilon > 0 \),

\[
P \left\{ \left\|n^{-1/2} \sum_{i=1}^{n} (\hat{g}_{n,i} - g_{n,i}) \right\| \geq \varepsilon \left| X_1, \ldots, X_n \right. \right\} = o_p(1),
\]

which implies (30) due to the dominated convergence theorem.

Denote \( \varepsilon_u = n^{-1} \sum_{i=1}^{n} \left\{ \hat{g}_{n,i} \hat{g}_{n,i}^T - g_{n,i} g_{n,i}^T \right\} u \). Then we have \( E\{ (\varepsilon_u^j)^2 | X_1, \ldots, X_n \} \leq O_p(r_n^3 n^{-2}) \) uniformly for \( u \) and \( j \). Therefore, \( E\{ \| \varepsilon_u \|^2 | X_1, \ldots, X_n \} \leq O_p(r_n^4 n^{-2}) \leq o_p(1) \), which implies (31).

\( \square \)

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Table 1. Bias and Standard Error Comparisons When Logit is Linear in X.

| Method   | True $\beta$ | MC Bias | OptStd | MC Std | CovProb | avlen |
|----------|--------------|---------|--------|--------|---------|-------|
|          | $X \sim N(0, 0.5^2)$ |         |        |        |         |       |
| marginal | 0.2832       | 0.0033  | 0.1992 | 0.2025 | 0.9520  | 0.7960 |
|          | 0.6096       | 0.0063  | 0.2872 | 0.3007 | 0.9486  | 1.1801 |
| 5 Fourier| 0.2832       | 0.0036  | 0.1992 | 0.2027 | 0.9500  | 0.7870 |
|          | 0.6096       | 0.0056  | 0.2872 | 0.2968 | 0.9468  | 1.1536 |
|          | $X \sim N(0, 1^2)$ |         |        |        |         |       |
| marginal | 0.2479       | 0.0010  | 0.1929 | 0.2025 | 0.9520  | 0.7940 |
|          | 0.4634       | 0.0063  | 0.2585 | 0.2988 | 0.9472  | 1.1562 |
| 5 Fourier| 0.2479       | 0.0011  | 0.1929 | 0.1992 | 0.9496  | 0.7718 |
|          | 0.4634       | 0.0049  | 0.2585 | 0.2812 | 0.9424  | 1.0785 |
|          | $X \sim N(0, 2^2)$ |         |        |        |         |       |
| marginal | 0.1814       | 0.0040  | 0.1800 | 0.1995 | 0.9526  | 0.7912 |
|          | 0.2792       | 0.0003  | 0.2110 | 0.2951 | 0.9452  | 1.1324 |
| 5 Fourier| 0.1814       | 0.0043  | 0.1800 | 0.1873 | 0.9518  | 0.7337 |
|          | 0.2792       | -0.0018 | 0.2110 | 0.2439 | 0.9418  | 0.9292 |
| 7 Fourier| 0.1814       | 0.0030  | 0.1800 | 0.1860 | 0.9494  | 0.7186 |
|          | 0.2792       | 0.0008  | 0.2110 | 0.2341 | 0.9442  | 0.8846 |
| 9 Fourier| 0.1814       | 0.0032  | 0.1800 | 0.1857 | 0.9464  | 0.7101 |
|          | 0.2792       | 0.0008  | 0.2110 | 0.2311 | 0.9384  | 0.8631 |
| 11 Fourier| 0.1814     | 0.0032  | 0.1800 | 0.1852 | 0.9448  | 0.7037 |
|          | 0.2792       | 0.0007  | 0.2110 | 0.2293 | 0.9340  | 0.8490 |

NOTE: In all the tables, ‘marginal’ means using empirical likelihood method with 2 marginal estimating equations $Y - \phi(\beta_1 + \beta_2 Z)$ and $Z \left( Y - \phi(\beta_1 + \beta_2 Z) \right)$, while “5 Fourier” has three additional estimating equations $2Z - 1$, $\sqrt{2}(2Z - 1) \sin[2\pi F_n(X)]$ and $\sqrt{2}(2Z - 1) \cos[2\pi F_n(X)]$, where $F_n(X)$ is the empirical cumulative distribution function of X. MC Bias is Monte Carlo bias, OptStd is the asymptotic standard error obtained according to the sandwich formula, MC Std is the Monte Carlo standard error, CovProb is the coverage probability of 95% Wald confidence intervals and avlen is the average length of those confidence intervals.
Table 2. Bias and Standard Error Comparisons When Logit is Quadratic in X.

| Method   | True $\beta$ | MC Bias | OptStd | MC Std | CovProb | avlen |
|----------|---------------|---------|--------|--------|---------|-------|
|          | $X \sim N(0, 0.5^2)$ |         |        |        |         |       |
| marginal | 0.5298        | 0.0057  | 0.2059 | 0.2093 | 0.9516  | 0.8160|
|          | 0.7758        | 0.0094  | 0.3169 | 0.3266 | 0.9536  | 1.2683|
| 5 Fourier| 0.5298        | 0.0061  | 0.2059 | 0.2088 | 0.9480  | 0.8090|
|          | 0.7758        | 0.0088  | 0.3169 | 0.3257 | 0.9524  | 1.2523|
|          | $X \sim N(0, 1^2)$ |         |        |        |         |       |
| marginal | 0.9664        | 0.0106  | 0.2182 | 0.2307 | 0.9476  | 0.8845|
|          | 0.8105        | 0.0182  | 0.3466 | 0.3795 | 0.9494  | 1.4450|
| 5 Fourier| 0.9664        | 0.0111  | 0.2182 | 0.2254 | 0.9448  | 0.8604|
|          | 0.8105        | 0.0156  | 0.3466 | 0.3648 | 0.9502  | 1.3800|

Table 3. Bias and Standard Error Comparisons When Logit Contains Two Covariates.

| Method   | True $\beta$ | MC Bias | OptStd | MC Std | CovProb | avlen |
|----------|---------------|---------|--------|--------|---------|-------|
|          | $X_1 \sim N(0, 1^2), X_2 \sim N(0, 2^2)$ |         |        |        |         |       |
| marginal | 0.1061        | -0.0003 | 0.1649 | 0.2005 | 0.9558  | 0.7883|
|          | 0.3157        | 0.0043  | 0.1828 | 0.2933 | 0.9494  | 1.1282|
| 7 Fourier| 0.1061        | -0.0009 | 0.1649 | 0.1761 | 0.9526  | 0.6813|
|          | 0.3157        | 0.0051  | 0.1828 | 0.2311 | 0.9438  | 0.8716|
|          | $X_1 \sim N^2(0, 1^2), X_2 \sim N(0, 2^2)$ |         |        |        |         |       |
| marginal | 0.4389        | 0.0063  | 0.1688 | 0.2032 | 0.9550  | 0.8069|
|          | 0.5493        | 0.0056  | 0.1985 | 0.3072 | 0.9486  | 1.2023|
| 7 Fourier| 0.4389        | 0.0052  | 0.1688 | 0.1825 | 0.9494  | 0.7012|
|          | 0.5493        | 0.0041  | 0.1985 | 0.2490 | 0.9458  | 0.9396|
|          | $X_1 \sim N^2(0, 0.5^2), X_2 \sim N^2(0, 1^2)$ |         |        |        |         |       |
| marginal | 1.4746        | 0.0149  | 0.2482 | 0.2594 | 0.9562  | 1.0201|
|          | 0.5813        | 0.0233  | 0.3857 | 0.4310 | 0.9498  | 1.6363|
| 7 Fourier| 1.4746        | 0.0144  | 0.2482 | 0.2512 | 0.9518  | 0.9771|
|          | 0.5813        | 0.0224  | 0.3857 | 0.4126 | 0.9486  | 1.5485|

NOTE: The logit is either quadratic ($X \sim N^2(\cdot, \cdot)$) or linear ($X \sim N(\cdot, \cdot)$) in each covariate.
Table 4. Power Comparison When Logit is Linear in X.

| X         | $\beta_{10}$ | $\beta_{20}$ | CovProb | Power | CovProb | Power |
|-----------|--------------|--------------|---------|-------|---------|-------|
| $N(0, 0.5^2)$ | 0.2125       | 0.8304       | 0.9498  | 0.7928 | 0.9492  | 0.8216 |
| $N(0, 1^2)$  | 0.1379       | 0.8207       | 0.9494  | 0.7826 | 0.9458  | 0.8682 |
| $N(0, 2^2)$  | 0.0386       | 0.8182       | 0.9486  | 0.7938 | 0.9436  | 0.9568 |

Table 5. Power Comparison When Logit is Quadratic in X.

| X         | $\beta_{10}$ | $\beta_{20}$ | CovProb | Power | CovProb | Power |
|-----------|--------------|--------------|---------|-------|---------|-------|
| $N(0, 0.5^2)$ | 0.8511       | 1.0599       | 0.9442  | 0.8428 | 0.9448  | 0.8498 |
| $N(0, 1^2)$  | 0.9662       | 0.9359       | 0.9464  | 0.7356 | 0.9482  | 0.7724 |

Table 6. Power Comparison When Logit Contains Two Covariates.

| X, X | $\beta_{10}$ | $\beta_{20}$ | CovProb | Power | CovProb | Power |
|------|--------------|--------------|---------|-------|---------|-------|
| $N(0, 1^2), N(0, 2^2)$ | 0.0694       | 0.8461       | 0.9488  | 0.8166 | 0.9430  | 0.9308 |
| $N^2(0, 1^2), N(0, 2^2)$ | 0.2468       | 0.7012       | 0.9418  | 0.6584 | 0.9438  | 0.8636 |
| $N^2(0, 0.5^2), N^2(0, 1^2)$ | 1.1701       | 0.8342       | 0.9496  | 0.5873 | 0.9478  | 0.6140 |

NOTE: In each scenario, $\beta_{10}$ and $\beta_{20}$ are the true values. The profile empirical likelihood ratio test is used to test the null hypothesis $H_0: \beta_2 = 0$. CovProb are the coverage probabilities of tests $\beta_2 = \beta_{20}$. 