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Jackknife empirical likelihood method for case-control studies with gene-environment independence on controls

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In this paper, we propose a jackknife empirical likelihood method to do inference for the interested parameters of the multiplicative-intercept risk models by taking into account the gene-environment independence on controls in case-control studies. It is shown that the proposed statistic is asymptotically chi-squared distributed. Simulation studies investigate the small-sample properties. A real example is also given.

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1. INTRODUCTION

The case-control study, where sampling is conditioned on the presence (cases) and absence (controls) of a disease, is an efficient way of studying the effect of risk factors to rare diseases. As the regression coefficients have a desired interpretation in terms of log-odds ratios which are estimable based on case-control samples, logistic regression models have been widely applied to analyze binary data arising from case-control studies in epidemiology (see, e.g., Breslow, 1996).

To be precise, suppose that D is a binary response variable of presence ($D=1$), or absence ($D=0$) of a disease, and X is the associated explanatory variables. We consider the general logistic regression model, also known as the multiplicative-intercept risk model:

$$P(D=1|X=x)=\frac{\exp\{\alpha^*+m(x,\beta)\}}{1+\exp\{\alpha^*+m(x,\beta)\}}, \tag{1}$$

where $m(x,\beta)$ is a given function, α^* is a scale parameter, $\beta=(\beta_1,\dots,\beta_p)^T$ is a p-vector parameter, and the marginal distribution of X is unspecified. As in Prentice and Pyke (1979), the case-control samples are two independent groups of samples based on model (1), i.e., $X_1,\dots,X_{n_0}$ are a random sample (controls) from $P(x|D=0)$ and $X_{n_0+1},\dots,X_n$ are another random sample (cases) from $P(x|D=1)$.

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Let $f(x|D=0)$ and $f(x|D=1)$ be the conditional density functions of the controls and cases. Under the logistic assumptions, it can be shown that

$$f(x|D=1)=f(x|D=0)\exp\{\alpha+m(x,\beta)\},$$

where $\alpha=\alpha^*+\log\{P(D=0)/P(D=1)\}$. Therefore, model (1) is equivalent to the following two-sample semiparametric density ratio model:

(2) $X_1,\dots,X_{n_0}$ are independent with density $f(x|D=0)$, $X_{n_0+1},\dots,X_n$ are independent with density $\exp\{\alpha+m(x,\beta)\}f(x|D=0)$.

Notice that model (2) is considerably flexible. For example, it is a biased sampling model with weight function $\exp\{\alpha+m(x,\beta)\}$, where α and β are unknown (see, e.g., Vardi, 1982; Gill et al., 1988; Qin, 1993). If $m(x,\beta)=\beta^Tx$ with x being a $p\times 1$ random vector, model (2) reduces to the standard logistic model (see, e.g., Anderson, 1979; Breslow and Day, 1980). Model (2) is also related to the Cox proportional hazards model (see, Qin, 1998).

There is extensive literature on model (2) under the case-control sampling plans. For example, O'Neill (1980) studied the discrimination problem in (2); Cox and Ferry (1991) and Weinberg and Wacholder (1993) investigated this model mainly for discrete data; Qin (1998) employed empirical likelihood to model (2), derived the asymptotic normality and further showed the optimality in the sense of Godambe (1960). Related work also has been done for the standard logistic regression model, references include Prentice and Pyke (1979), Anderson and Blair (1982), Wang and Carroll (1993), Qin and Zhang (1997), and Brelsow et al. (2000) among others.

Our research is motivated by epidemiological studies on gene-environment interaction problems. As the genetic susceptibility and environmental (or non-genetic) exposures play an interactive role in aetiology of many diseases, epidemiologists often seek to examine how these two risk factors affect a disease through case-control studies. Intuitively, an individual's genetic susceptibility is determined since birth, and may not relate to his/her environmental exposures. Recent studies showed that the assumption of independence between gene and environmental exposures may be reasonable; see Hwang et al. (1994) for example. This has attracted some researchers' attention, and they have developed new methods for analyzing case-control data in these occasions; see Piegorsch et al. (1994), Umbach and Weinberg (1997), Modan et al. (2001). However, all these methods have their own drawbacks, see Chatterjee and Carroll (2005) for more discussion. For instance, Chatterjee and Carroll (2005) considered the case-control problem when the underlying populations satisfy gene-environment independence but assume that the populations contain only finite values. Thus, seeking a novel method to this case becomes important.

As pointed out by Piegorsch et al. (1994), assumptions that genotype and exposure are independent in the population and that the disease is rare, in fact, imply that genotype and exposure are (approximately) independent in the non-diseased population. Naturally, a method that could make full use of such information will invariably increase efficiency. It is well-known that empirical likelihood approach of Owen (1988, 1990, 2001) can easily incorporate such information in the model, in addition to its many other nice properties. In fact, the empirical likelihood to case-control studies has been investigated by Qin (1998) when there is no auxiliary information. When applying the procedure of Qin (1998) to profile out the nuisance parameters, unfortunately, this method does not produce a closed form for this problem.

To overcome the difficulties encountered by Owen's direct application of empirical likelihood, we consider the jackknife empirical likelihood (JEL) method, proposed recently by Jing, Yuan and Zhou (2009). The idea of the JEL is to construct a jackknife pseudo-values first, and then treat this jackknife pseudo-sample as a sample of i.i.d. observations and apply the standard empirical likelihood method for the mean of the jackknife pseudo-sample to obtain the empirical likelihood ratio statistic. In this paper, we study the possibility of extending the jackknife empirical likelihood method to the case-control studies taking into consideration the gene-environment independence on controls.

We organize this paper as follows. Section 2 gives the detailed methodology and main results. A simulation study is presented in Section 3. All proofs are put in Section 4.

2. MAIN RESULTS

2.1 Formulation

Suppose that one has auxiliary information of the gene-environment independence on controls, i.e., for $x_i = (x_{i,1}, x_{i,2})$, we have

$$f(x_{i,1}, x_{i,2}|D=0) = f(x_{i,1}|D=0)f(x_{i,2}|D=0).$$

Define

$$\begin{aligned} p_{i,1} &= dF(x_{i,1}|D=0), \quad i = 1, \ldots, n_0, \\ p_{i,2} &= dF(x_{i,2}|D=0), \quad i = 1, \ldots, n_0, \\ q_k &= dF(x_{k,1}, x_{k,2}|D=1), \quad k = n_0+1, \ldots, n. \end{aligned}$$

The log-empirical likelihood function is defined as

$$(3) \qquad \begin{aligned} L(\alpha,\beta) &= \log\left(\prod_{i=1}^{n_0}(p_{i,1}p_{i,2}) \prod_{k=n_0+1}^{n} q_k\right) \\ &= \sum_{j=1}^{2}\sum_{i=1}^{n_0} \log p_{i,j} + \sum_{k=n_0+1}^{n} \log q_k \end{aligned}$$

subject to the constraints

$$(4) \qquad \sum_{i=1}^{n_0} p_{i,j} = 1 \quad \text{and} \quad \sum_{k=n_0+1}^{n} q_k = 1, \quad p_{i,j}, q_k \geq 0, \; j=1,2,$$

and

$$(5) \qquad \sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} p_{i_1,1}p_{i_2,2}[\exp\{\alpha + m(X_{i_1,1}, X_{i_2,2}, \beta)\} - 1] = 0,$$

$$(6) \qquad \sum_{k=n_0+1}^{n} q_k[\exp\{-\alpha - m(X_{k,1}, X_{k,2}, \beta)\} - 1] = 0.$$

The constraints (5) and (6) come respectively from

$$\begin{aligned} 1 &= \int f(x_i|D=1)dx_i = \int \exp\{\alpha + m(x_i,\beta)\}dF(x_i|D=0) \\ &= \int \exp\{\alpha + m(x_i,\beta)\}dF(x_{i,1}|D=0)dF(x_{i,2}|D=0), \end{aligned}$$

and

$$1 = \int f(x_i|D=0)dx_i = \int \exp\{-\alpha - m(x_i,\beta)\}dF(x_i|D=1).$$

2.2 Jackknife empirical likelihood

Due to its highly nonlinear nature of the (5) and (6), direct application of Owen's empirical likelihood will encounter some serious computational difficulties. To overcome this, we consider using the jackknife empirical likelihood method, proposed by Jing, Yuan and Zhou (2009). To do this, we define $n_1 = n - n_0$,

$$\begin{aligned} U_1(\alpha,\beta) &= \frac{1}{n_0^2}\sum_{i=1}^{n_0}\sum_{j=1}^{n_0} h_1(X_{i,1}, X_{j,2}; \alpha, \beta), \\ U_2(\alpha,\beta) &= \frac{1}{n_1}\sum_{k=1}^{n_1} h_2(X_{n_0+k}; \alpha, \beta) \end{aligned}$$

with respective kernels

$$\begin{aligned} h_1(X_{i,1}, X_{j,2}; \alpha, \beta) &= \exp\{\alpha + m(X_{i,1}, X_{j,2}, \beta)\} - 1, \\ h_2(X_k; \alpha, \beta) &= \exp\{-\alpha - m(X_{k,1}, X_{k,2}, \beta)\} - 1. \end{aligned}$$

Note that $U_1(\alpha, \beta)$ is a two-sample U-statistic while $U_2(\alpha, \beta)$ is a one-sample U-statistic.

However, $U_1(\alpha,\beta)$ can be rewritten expressed as a one-sample U-statistic:

$$U_1(\alpha,\beta) = \binom{2n_0}{2}^{-1} \sum_{1\le i<j\le 2n_0} H_1(Z_{1,i}, Z_{1,j}; \alpha,\beta),$$

where

$$Z_{1,i} = \begin{cases} X_{i,1}, & i=1,\dots,n_0,\\ X_{i-n_0,2}, & i=n_0+1,\dots,2n_0,\end{cases}$$

$$H_1(Z_{1,i}, Z_{1,j}; \alpha,\beta) = \begin{cases} (2n_0-1)h_1(Z_{1,i}, Z_{1,j}; \alpha,\beta)/n_0, \\ \qquad 1\le i\le n_0<j\le 2n_0, \\ 0, \quad \text{otherwise}.\end{cases}$$

Define the jackknife pseudo-values by

$$\widehat{V}_{1i}(\alpha,\beta) = 2n_0U_1(\alpha,\beta) - (2n_0-1)U_1^{(-i)}(\alpha,\beta), \quad i=1,\dots,2n_0, \tag{7}$$

$$\widehat{V}_{2k}(\alpha,\beta) = n_1U_2(\alpha,\beta) - (n_1-1)U_2^{(-k)}(\alpha,\beta), \quad k=1,\dots,n_1, \tag{8}$$

where $U_1^{(-i)}$ is calculated from U_1 using $Z_{1,1},\dots,Z_{1,i-1}$, $Z_{1,i+1},\dots,Z_{1,2n_0}$ after deleting the ith data value $Z_{1,i}$ while $U_2^{(-k)}$ is computed from $X_{n_0+1},\dots,X_{n_0+k-1}$, $X_{n_0+k+1},\dots,X_n$ after deleting the kth data value X_{n_0+k}. It can be seen that

$$U_1(\alpha,\beta) = \frac{1}{2n_0}\sum_{i=1}^{2n_0} \widehat{V}_{1i}(\alpha,\beta),$$

$$U_2(\alpha,\beta) = \frac{1}{n_1}\sum_{j=1}^{n_1} \widehat{V}_{2j}(\alpha,\beta).$$

Since jackknife pseudo-values are asymptotically independent (see, Shi, 1984), we can treat $\{\widehat{V}_{1i}(\alpha,\beta), i=1,\dots,2n_0\}$ as one sample, while $\{\widehat{V}_{2i}(\alpha,\beta), i=1,\dots,n_1\}$ (i.e., $h_2(Z_{2,i};\alpha,\beta), i=1,\dots,n_1$) is another i.i.d. sample. Define

$$p_i = dF(\widehat{V}_{1i}(\alpha,\beta)|D=0), \quad \text{and} \quad q_j = dF(\widehat{V}_{2j}(\alpha,\beta)|D=1).$$

Then the empirical log-likelihood of those pseudo-values can be re-defined as

$$L(\alpha,\beta) = \sum_{i=1}^{2n_0}\log p_i + \sum_{j=1}^{n_1}\log q_j,$$

subject to the constraints

$$\begin{cases} \sum_{i=1}^{2n_0} p_i = 1, \quad \sum_{j=1}^{n_1} q_j = 1, \quad p_i, q_j \ge 0,\\ \sum_{i=1}^{2n_0} p_i\widehat{V}_{1i}(\alpha,\beta) = 0,\\ \sum_{j=1}^{n_1} q_j\widehat{V}_{2j}(\alpha,\beta) = 0.\end{cases}$$

Using the Lagrange multiplier method, we have that $L(\alpha,\beta)$ attains its maximum at

$$p_i = \frac{1}{2n_0}\cdot\frac{1}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta)}, \quad \text{and} \quad q_j = \frac{1}{n_1}\cdot\frac{1}{1+\lambda_2\widehat{V}_{2j}(\alpha,\beta)}.$$

This, in turn, gives the $-2\times$ log-likelihood ratio as

$$l(\alpha,\beta) = 2\sum_{i=1}^{2n_0}\log\{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta)\} + 2\sum_{j=1}^{n_1}\log\{1+\lambda_2\widehat{V}_{2j}(\alpha,\beta)\},$$

where λ_1 and λ_2 satisfy

$$Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2) := \frac{1}{2n_0}\sum_{i=1}^{2n_0}\frac{\widehat{V}_{1i}(\alpha,\beta)}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta)} = 0, \tag{9}$$

$$Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2) := \frac{1}{n_1}\sum_{j=1}^{n_1}\frac{\widehat{V}_{2j}(\alpha,\beta)}{1+\lambda_2\widehat{V}_{2j}(\alpha,\beta)} = 0. \tag{10}$$

Since we are interested in β, we minimize $l(\alpha,\beta)$ with respect to α and obtain the profile likelihood ratio

$$l(\beta) = 2\sum_{i=1}^{2n_0}\log\{1+\lambda_1\widehat{V}_{1i}(\hat\alpha,\beta)\} + 2\sum_{j=1}^{n_1}\log\{1+\lambda_2\widehat{V}_{2j}(\hat\alpha,\beta)\}, \tag{11}$$

where $\hat\alpha = \arg\min_\alpha l(\alpha,\beta)$.

2.3 Main results

Before stating the main results, we list two assumptions:

Assumption 1. $\lim_{n_0,n_1\to\infty} n_1/2n_0 = \rho < \infty$, and denote α_0 and β_0 as the true values of α and β, respectively.

Assumption 2. $h_1(X_1,X_2;\alpha,\beta_0)$ and $h_2(X;\alpha,\beta_0)$ are bounded by some integrable function $G(X_1,X_2)$ for $|\alpha-\alpha_0|\le n_0^{-1/3}$.

Our main results are as follows:

Proposition 1. *Assume that Assumptions 1–2 hold. Then, with probability tending to one, $l(\alpha,\beta_0)$ attains its minimum at some point $\hat\alpha$ in the interior of $|\alpha-\alpha_0|\le n_0^{-1/3}$. Moreover, $\hat\alpha$, λ_1 and λ_2 in (11) satisfy (9), (10) and*

$$Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2) := \frac{1}{2n_0}\sum_{i=1}^{2n_0}\frac{\lambda_1\partial\widehat{V}_{1i}(\alpha,\beta_0)/\partial\alpha}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)} + \frac{1}{2n_0}\sum_{j=1}^{n_1}\frac{\lambda_2\partial\widehat{V}_{2j}(\alpha,\beta_0)/\partial\alpha}{1+\lambda_2\widehat{V}_{2j}(\alpha,\beta_0)} = 0. \tag{12}$$

Theorem 1. *Assume that Assumptions 1–2 hold. We have $l(\hat\alpha,\beta_0)\xrightarrow{d}\chi_1^2$, as $n\to\infty$, where $\hat\alpha$ is given in Proposition 1.*

From Theorem 1, a confidence interval of β_0 with level γ can be obtained as

$$I_\gamma(r) = \{\beta : l(\hat{\alpha}, \beta) \le \chi^2_{1,\gamma}\},$$

where $\chi^2_{1,\gamma}$ is the γth quantile of χ^2_1.

3. SIMULATIONS

In this section, we conduct a simulation study to evaluate the finite sample performances of the proposed jackknife empirical likelihood confidence interval for the interested parameters. We consider the following experiment, the components of the controls are independent with $X_{1,1} \sim N(\mu_1, (1-\rho^2)\sigma_1^2)$ and $X_{1,2} \sim N(\mu_2, (1-\rho^2)\sigma_2^2)$, while two components of the cases are not independent and follow a bivariate normal distribution, i.e., $(Y_{1,1}, Y_{1,2}) \sim BN(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$. That is,

$$\begin{aligned} f(x_1, x_2|D=0) &= \frac{1}{\sqrt{2\pi}\sigma_1\sqrt{1-\rho^2}} \exp\left\{-\frac{(x_1-\mu_1)^2}{2(1-\rho^2)\sigma_1^2}\right\} \\ &\quad \times \frac{1}{\sqrt{2\pi}\sigma_2\sqrt{1-\rho^2}} \exp\left\{-\frac{(x_2-\mu_2)^2}{2(1-\rho^2)\sigma_2^2}\right\}, \\ f(x_1, x_2|D=1) &= \exp\{\alpha + m(x, \beta)\} f(x_1, x_2|D=0), \end{aligned}$$

where

$$\begin{aligned} \alpha &= \log\sqrt{1-\rho^2} + \frac{\rho\mu_1\mu_2}{(1-\rho^2)\sigma_1\sigma_2}, \\ m(x_1, x_2, \beta) &= \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2 \\ &= -\frac{\rho\mu_2}{(1-\rho^2)\sigma_1\sigma_2} x_1 - \frac{\rho\mu_1}{(1-\rho^2)\sigma_1\sigma_2} x_2 \\ &\quad + \frac{\rho}{(1-\rho^2)\sigma_1\sigma_2} x_1 x_2. \end{aligned}$$

In our simulation, we consider $\rho = 0.2$ and 0.5. For each setup, we put $\mu_1 = 1$, $\mu_2 = 0.5$, $\sigma_1 = \sigma_2 = 1$, and generate 1,000 cases and 1,000 controls with sample sizes $n_0 = n_1 = 20$, 40, 70, respectively. We employ the package 'emplik' in the software R to compute the coverage probabilities of the proposed jackknife empirical likelihood method.

For comparisons, we also computed the coverage probabilities of the logistic regression method not using the independent information in controls while they actually have, i.e., all of the setup are the same as before, and the cases and controls are corresponding to 1 and 0, respectively, we employ the R package "glm" to do the logistic regression. Thus, the confidence region for $\beta = (\beta_1, \beta_2, \beta_3)$ with confidence level γ is given by

$$\{\hat{\beta} : (\hat{\beta} - \beta_0)^T \hat{\Sigma}^{-1} (\hat{\beta} - \beta_0) \le \chi^2_{3,\gamma}\},$$

where $\chi^2_{3,\gamma}$ is the γth quantile of χ^2_3. $\hat{\beta} = (\hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3)$ and the variance-covariance matrix $\hat{\Sigma}$ for $\hat{\beta}$ can be obtained through the package simultaneously.

In Table 1, we report the coverage probabilities of the 90% and 95% confidence regions for β_0 using JEL and logistic regression. From these simulation results, we observe:

Table 1. Coverage probabilities of the 90% and 95% confidence intervals for $(\beta_1, \beta_2, \beta_3)$

(n_0, n_1, ρ)	JEL		Logistic	
	$\gamma = 0.90$	$\gamma = 0.95$	$\gamma = 0.90$	$\gamma = 0.95$
$(20, 20, 0.2)$	0.863	0.927	0.965	0.991
$(20, 20, 0.5)$	0.865	0.914	0.957	0.989
$(40, 40, 0.2)$	0.877	0.937	0.934	0.977
$(40, 40, 0.5)$	0.865	0.927	0.919	0.967
$(70, 70, 0.2)$	0.882	0.938	0.912	0.968
$(70, 70, 0.5)$	0.901	0.952	0.889	0.954

- As sample size increases, the coverage probabilities in both cases converge to the nominal levels.
- The JEL method performs better than logistic regression method which does not use the independence among controls in most cases.
- The JEL tends to have under-coverage probabilities while the logistic regression tend to have over-coverage probabilities. However, over-coverage probabilities are usually achieved by too wide confidence regions, which are less desirable.

4. A REAL EXAMPLE

We apply our method to the data set of Cameron and Pauling (1978). See Table 33.1 in Andrew and Herzberg (1985). The survival times of 100 terminal cancer patients (cases) and $1,000$ matched controls were recorded. To be specific, the treated group of 100 patients with terminal cancer of various kinds began ascorbate treatment, while the controls received the same treatment as the treated group except for the ascorbate. This data set comprises the survival times of the ascorbate-treated patients after the date of first hospital attendance for the cancer that became untreatable, their survival times measured from the dates of untreatability, and the corresponding mean values for the matched controls. We are interested in whether supplemental ascorbate prolongs the survival times of patients with terminal cancer, and we use JEL to estimate the parameters involved. We consider $m(x, \beta) = m(x_1, x_2, \beta)$ in (1) as

$$m(x, \beta) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2 + \beta_4 x_1^2.$$

References on density ratio model selection include Qin and Zhang (1997), Fokianos (2007), among others. The survival times of patients of stomach cancer and breast cancer (Table 33.1) were selected for illustrating purposes. Here we transform the survival times in days to years, i.e., $\cdot/365$, and exclude two patients who were alive on 15 May 1978.

From Table 2, we observe that the confidence intervals of β_3 do not include 0. Then, the supplemental ascorbate impacts the survival times of patients with terminal human

Table 2. 90% *and* 95% *confidence intervals for* $(\beta_1, \beta_2, \beta_3, \beta_4)$

β	I Stomach $\gamma = 0.90$	$\gamma = 0.95$
β_1	$(-59.24426, -58.34373)$	$(-59.28645, -57.86839)$
β_2	$(70.54456, 71.44511)$	$(70.50234, 71.92042)$
β_3	$(-14.94648, -14.04593)$	$(-14.98869, -13.57061)$
β_4	$(17.56186, 18.46241)$	$(17.51964, 18.93772)$

β	II Breast $\gamma = 0.90$	$\gamma = 0.95$
β_1	$(-4.0041133, -3.9136229)$	$(-4.0065935, -3.9077849)$
β_2	$(13.1403123, 13.2308033)$	$(13.1378322, 13.2366412)$
β_3	$(-1.6815360, -1.5910451)$	$(-1.6840162, -1.5852071)$
β_4	$(0.6463878, 0.7368786)$	$(0.6439076, 0.7427167)$

cancer. So, the proposed method is helpful for practical data analysis in case control studies.

5. PROOFS

For simplicity, we give some notations. Put

$$\begin{cases} U_l(\alpha) = U_l(\alpha, \beta_0), \quad l = 1,2 \\ \bar{U}_1^2(\alpha) = \frac{1}{2n_0}\sum_{i=1}^{2n_0} \widehat{V}_{1i}^2(\alpha, \beta_0) \\ \bar{U}_2^2(\alpha) = \frac{1}{n_1}\sum_{j=1}^{n_1} \widehat{V}_{2j}^2(\alpha, \beta_0) \\ U_1^0(\alpha) : \text{the original statistics based on } X_1, \dots, X_{n_0} \\ \text{For } i = 1, \dots, n_0, \\ U_1^{-i,0}(\alpha) : \text{the statistics after deleting } X_{i,1} \\ V_{1,i0}(\alpha) = n_0 U_1^0(\alpha) - (n_0 - 1)U_1^{-i,0}(\alpha) \\ \text{For } j = 1, \dots, n_0, \\ U_1^{0,-j}(\alpha) : \text{the statistics after deleting } X_{j,2}, \\ V_{1,0j}(\alpha) = n_0 U_1^0(\alpha) - (n_0 - 1)U_1^{0,-j}(\alpha) \\ g_{1,10}(x; \alpha, \beta_0) = Eh_1(x, X_{1,2}; \alpha, \beta_0) \\ \sigma_{1,10}^2(\alpha) = Var(g_{1,10}(X_{1,1}; \alpha, \beta_0)) \\ g_{1,01}(y; \alpha, \beta_0) = Eh_1(X_{1,1}, y; \alpha, \beta_0) \\ \sigma_{1,01}^2(\alpha) = Var(g_{1,01}(X_{1,2}; \alpha, \beta_0)). \end{cases}$$

It is known that the consistent estimator of $Var(U_1(\alpha))$ is (see Arvesen, 1969)

$$\widehat{Var}_{Jack}(U_1(\alpha)) = \frac{1}{n_0(n_0-1)}\sum_{i=1}^{n_0}(V_{1,i0}(\alpha) - \bar{V}_{1,\bullet 0}(\alpha))^2 + \frac{1}{n_0(n_0-1)}\sum_{j=1}^{n_0}(V_{1,0j}(\alpha) - \bar{V}_{1,0\bullet}(\alpha))^2$$

where $\bar{V}_{1,\bullet 0}(\alpha)$ and $\bar{V}_{1,0\bullet}(\alpha)$ are the averages of $V_{1,i0}(\alpha)$ and $V_{1,0i}(\alpha)$, respectively. From Schechtman and Schechtman (2002), we have

$$\bar{V}_{1,\bullet 0}(\alpha) = U_1(\alpha), \qquad \bar{V}_{1,0\bullet}(\alpha) = U_1(\alpha).$$

For $i = 1, \dots, 2n_0$, $j = 1, \dots, n_1$, it can be verified that

$$\frac{\partial \widehat{V}_{1i}(\alpha)}{\partial \alpha} = \widehat{V}_{1i}(\alpha) + 1, \qquad \frac{\partial \widehat{V}_{2j}(\alpha)}{\partial \alpha} = -\widehat{V}_{2j}(\alpha) - 1. \tag{13}$$

First we list some lemmas.

Lemma 1. *Under the conditions of Proposition 1, and if* $\sigma_{1,10}^2(\alpha), \sigma_{1,01}^2(\alpha) > 0$, *for each* α *such that* $|\alpha - \alpha_0| \le n_0^{-1/3}$. *Then as* $n_0, n_1 \to \infty$, *we have*

$$\begin{cases} n_0^{1/2} U_1(\alpha_0) \xrightarrow{d} N(0, S_1^2) \\ n_1^{1/2} U_2(\alpha_0) \xrightarrow{d} N(0, S_2^2) \\ \bar{U}_1^2(\alpha_0) = S_1^2 + o_p(1) \\ \bar{U}_2^2(\alpha_0) = S_2^2 + o_p(1), \end{cases}$$

where $S_1^2 = 2(\sigma_{1,10}^2(\alpha_0) + \sigma_{1,01}^2(\alpha_0))$, $S_2^2 = Eh_2^2(X_{n_0+1}; \alpha_0, \beta_0)$.

Proof. The first one is from Arvesen (1969), while the second one comes from the central limit theorem. Now, we prove that $\bar{U}_1^2(\alpha_0) = S_1^2 + o_p(1)$. For $i = 1, \dots, n_0$, it can be checked that

$$\begin{aligned} \frac{1}{n_0}\sum_{i=1}^{n_0} \widehat{V}_{1i}^2(\alpha_0) &= \frac{1}{n_0}\sum_{i=1}^{n_0}\left[\frac{2n_0-1}{n_0-1}V_{1,i0}(\alpha_0) - \frac{n_0}{n_0-1}U_1(\alpha_0)\right]^2 \\ &= \left(\frac{2n_0-1}{n_0-1}\right)^2 \frac{1}{n_0}\sum_{i=1}^{n_0}[V_{1,i0}(\alpha_0) - U_1(\alpha_0)]^2 + U_1^2(\alpha_0), \end{aligned}$$

when $i = n_0 + 1, \dots, 2n_0$,

$$\begin{aligned} \frac{1}{n_0}\sum_{i=n_0+1}^{2n_0} \widehat{V}_{1(i-n_0)}^2(\alpha_0) &= \frac{1}{n_0}\sum_{i=n_0+1}^{2n_0}\left[\frac{2n_0-1}{n_0-1}V_{1,0(i-n_0)}(\alpha_0) - \frac{n_0}{n_0-1}U_1(\alpha_0)\right]^2 \\ &= \left(\frac{2n_0-1}{n_0-1}\right)^2 \frac{1}{n_0}\sum_{i=n_0+1}^{2n_0}[V_{1,0(i-n_0)}(\alpha_0) - U_1(\alpha_0)]^2 \\ &\quad + U_1^2(\alpha_0). \end{aligned}$$

Thus,

$$\bar{U}_1^2(\alpha) = \frac{1}{2}\frac{(2n_0-1)^2}{n_0-1}\left\{\frac{1}{n_0(n_0-1)}\sum_{i=1}^{n_0}[V_{1,i0}(\alpha_0) - U_1(\alpha_0)]^2 + \frac{1}{n_0(n_0-1)}\sum_{i=n_0+1}^{2n_0}[V_{1,0(i-n_0)}(\alpha_0) - U_1(\alpha_0)]^2\right\}$$

$$
\begin{aligned}
&\quad + U_1^2(\alpha_0) \\
&= 2(n_0-1)\,\widehat{Var}_{Jack}(U_1(\alpha_0)) + o_p(1) \\
&= S_1^2 + o_p(1),
\end{aligned}
$$

where the last equality comes from the fact that $\widehat{Var}_{Jack}(U_1(\alpha_0)) - n_0^{-1}(\sigma_{1,10}^2(\alpha_0) + \sigma_{1,01}^2(\alpha_0)) = o_p(n_0^{-1})$. Finally,

$$
\begin{aligned}
\bar{U}_2^2(\alpha_0) &= \frac{1}{n_1}\sum_{j=1}^{n_1} \widehat{V}_{2j}^2(\alpha_0) = \frac{1}{n_1}\sum_{j=1}^{n_1} h_2^2(X_{n_0+j};\alpha_0,\beta_0) \\
&\xrightarrow{p} Eh_2^2(X_{n_0+1};\alpha_0,\beta_0).
\end{aligned}
$$

Hence, we complete the proof. □

Lemma 2. *Under conditions of Proposition 1, if $\sigma_{1,10}^2(\alpha)$, $\sigma_{1,01}^2(\alpha) > 0$, for each $\alpha \in \Theta(\alpha_0)$, then as $n \to \infty$, we have*

$$
\begin{aligned}
P\Big(\min_{1\le i\le 2n_0} \widehat{V}_{1i}(\alpha) < 0 < \max_{1\le i\le 2n_0} \widehat{V}_{1i}(\alpha)\Big) \to 1, \\
P\Big(\min_{1\le j\le n_1} \widehat{V}_{2j}(\alpha) < 0 < \max_{1\le j\le n_1} \widehat{V}_{2j}(\alpha)\Big) \to 1.
\end{aligned}
$$

Proof. Note that

$$
\begin{aligned}
\widehat{V}_{1i}(\alpha) &= \frac{2n_0-1}{n_0-1}\{V_{1,i0}(\alpha)I(1\le i\le n_0) \\
&\quad + V_{1,0(i-n)}(\alpha)I(n_0+1\le i\le 2n_0)\} - \frac{n_0}{n_0-1}U_1(\alpha), \\
\widehat{V}_{2j}(\alpha) &= h_2(X_{n_0+j};\alpha_0,\beta_0) \\
&= \exp\{-\alpha_0 - m(X_{n_0+j},\beta)\} - 1.
\end{aligned}
$$

Following similar arguments to those of Jing et al. (2009), we can reach the conclusion. □

Lemma 3. *Under the conditions of Proposition 1, we have*

$$
\begin{cases}
U_1(\alpha) = O_p(n_0^{-1/3}) \\
U_2(\alpha) = O_p(n_0^{-1/3}) \\
\bar{U}_1^2(\alpha) = S_1^2 + o_p(1) \\
\bar{U}_2^2(\alpha) = S_2^2 + o_p(1),
\end{cases}
$$

where $O_p(\cdot)$ and $o_p(\cdot)$ hold uniformly for $\alpha \in \{\alpha : |\alpha-\alpha_0| \le n_0^{-1/3}\}$.

Proof. We only prove the cases of $U_1(\alpha)$ and $\bar{U}_1(\alpha)$. Applying Taylor expansion, and noting the fact (13), we have

(14)
$$
U_1(\alpha) = \frac{1}{2n_0}\sum_{i=1}^{2n_0}\widehat{V}_{1i}(\alpha_0) + \frac{1}{2n_0}\sum_{i=1}^{2n_0}[\widehat{V}_{1i}(\alpha^*)+1](\alpha-\alpha_0),
$$

where α^* is between α and α_0. As

$$
\begin{aligned}
\frac{1}{2n_0}\sum_{i=1}^{2n_0}\widehat{V}_{1i}(\alpha^*) &= \frac{1}{n_0^2}\sum_{i=1}^{n_0}\sum_{j=1}^{n_0} h_1(X_{i,1},X_{j,2};\alpha^*,\beta_0) \\
&\le \frac{1}{n_0^2}\sum_{i=1}^{n_0}\sum_{j=1}^{n_0} G(X_{i,1},X_{j,2}) \\
&\xrightarrow{p} E[G(X_{1,1},X_{1,2})] < \infty,
\end{aligned}
$$

this together with Lemma 1 leads to $U_1(\alpha) = O_p(n_0^{-1/3})$.

Next, let's look at $\bar{U}_1^2(\alpha)$. Notice that

$$
\begin{aligned}
&|\bar{U}_1^2(\alpha) - \bar{U}_1^2(\alpha_0)| \\
&= \left|\frac{1}{n_0}\sum_{i=1}^{2n_0}\widehat{V}_{1i}(\alpha^*)[\widehat{V}_{1i}(\alpha^*)+1](\alpha-\alpha_0)\right| \\
&\le \left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}(\alpha^*)[\widehat{V}_{1i}(\alpha^*)+1](\alpha-\alpha_0)\right| \\
&\quad + \left|\frac{1}{n_0}\sum_{i=n_0+1}^{2n_0}\widehat{V}_{1i}(\alpha^*)[\widehat{V}_{1i}(\alpha^*)+1](\alpha-\alpha_0)\right| \\
&:= A_1 + A_2.
\end{aligned}
$$

Now,

$$
\begin{aligned}
A_1 &= \left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}(\alpha^*)[\widehat{V}_{1i}(\alpha^*)+1](\alpha-\alpha_0)\right| \\
&\le \left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}^2(\alpha^*)(\alpha-\alpha_0)\right| + \left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}(\alpha^*)(\alpha-\alpha_0)\right| \\
&= \left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}^2(\alpha^*)\right| O_p(n_0^{-1/3}) + O_p(1)O_p(n_0^{-1/3}),
\end{aligned}
$$

while

$$
\begin{aligned}
&\left|\frac{1}{n_0}\sum_{i=1}^{n_0}\widehat{V}_{1i}^2(\alpha^*)\right| \\
&= \Bigg|\frac{1}{n_0}\sum_{i=1}^{n_0}\Bigg\{\frac{1}{n_0^2(n_0-1)^2} \\
&\quad \times \left[\sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} h_1(X_{i_1,1},X_{i_2,2};\alpha^*,\beta_0)\right]^2 \\
&\quad + \frac{(2n_0-1)^2}{n_0^2(n_0-1)^2}\left[\sum_{i_2=1}^{n_0} h_1(X_{i,1},X_{i_2,2};\alpha^*,\beta_0)\right]^2 \\
&\quad - \frac{2(2n_0-1)}{n_0^2(n_0-1)^2}\sum_{i_2=1}^{n_0} h_1(X_{i,1},X_{i_2,2};\alpha^*,\beta_0) \\
&\quad \times \sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} h_1(X_{i_1,1},X_{i_2,2};\alpha^*,\beta_0)\Bigg\}\Bigg| \\
&\le 4\left[\frac{1}{n_0^2}\sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} h_1(X_{i_1,1},X_{i_2,2};\alpha^*,\beta_0)\right]^2 \\
&\quad + \frac{9}{n_0}\sum_{i=1}^{n_0}\left[\frac{1}{n_0}\sum_{i_2=1}^{n_0} h_1(X_{i,1},X_{i_2,2};\alpha^*,\beta_0)\right]^2
\end{aligned}
$$

$$\le \frac{4}{n_0^2}\sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} h_1^2(X_{i_1,1},X_{i_2,2};\alpha^*,\beta_0)$$
$$+\frac{9}{n_0}\sum_{i=1}^{n_0}\frac{1}{n_0}\sum_{i_2=1}^{n_0} h_1^2(X_{i,1},X_{i_2,2};\alpha^*,\beta_0)$$
$$\le C\frac{1}{n_0^2}\sum_{i_1=1}^{n_0}\sum_{i_2=1}^{n_0} G(X_{i_1,1},X_{i_2,2})$$
$$\xrightarrow{p} CE(G(X_{i_1,1},X_{i_2,2}))<\infty.$$

Here, just use $(a+b)^2\le 2(a^2+b^2)$. Hence, $A_1=O_p(n_0^{-1/3})$. Similarly, we can prove that $A_2=O_p(n_0^{-1/3})$, which in turn implies $\bar{U}_1^2(\alpha)=\bar{U}_1^2(\alpha_0)+O_p(n_0^{-1/3})$. □

Lemma 4. *Let $J_1(\alpha)=\max_{1\le i\ne j\le 2n_0}|h_1(X_i,X_j;\alpha,\beta_0)|$, and $J_2(\alpha)=\max_{1\le i\le n_1}|h_2(X_{n_0+i};\alpha,\beta_0)|$. Then, under the conditions of Proposition 1, we have $J_l=o_p(n_0^{1/3})$, uniformly in $\alpha\in\{\alpha:|\alpha-\alpha_0|\le n_0^{-1/3}\}$.*

Proof. We only prove that $J_1(\alpha)=o_p(n_0^{1/3})$. By the chain argument, it suffices to prove that $3^{-n_0/3}\times\max_{1\le j<3^{n_0}}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\xrightarrow{p}0$. For each $\epsilon>0$, we have

$$\sum_{n_0=1}^{\infty} P\Big(\max_{\alpha}\max_{1\le j<3^{n_0}}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\ge \epsilon 3^{n_0/3}\Big)$$
$$\le \sum_{n_0=1}^{\infty} 3^{n_0}P\Big(\max_{\alpha}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\ge\epsilon 3^{n_0/3}\Big)$$
$$=\sum_{n_0=1}^{\infty}\sum_{m=n_0}^{\infty}3^{n_0}P(3^{(m+1)/3}>\epsilon^{-1}$$
$$\times\max_{\alpha}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\ge 3^{m/3})$$
$$=\sum_{m=1}^{\infty}\sum_{n_0=1}^{m}3^{n_0}P\Big(3^{(m+1)/3}>\epsilon^{-1}$$
$$\times\max_{\alpha}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\ge 3^{m/3}\Big)$$
$$\le\sum_{m=1}^{\infty}3^{m+1}P\Big(3^{(m+1)/3}>\epsilon^{-1}$$
$$\times\max_{\alpha}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\ge 3^{m/3}\Big)$$
$$\le 3\epsilon^{-3}E\max_{\alpha}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|^3$$
$$\le 3\epsilon^{-3}EG(X_{1,1},X_{1,2})<\infty.$$

Now, by the Borel-Cantelli lemma, with probability one, we have

$$3^{-n_0/3}\max_{1\le j<3^{n_0}}|h_1(X_{j,1},X_{3^{n_0},2};\alpha,\beta_0)|\to 0,$$

uniformly holds in α. □

Combining Lemmas 3 and 4, we have

$$(15)\qquad \begin{cases}\max_{1\le i\le 2n_0}|\widehat{V}_{1i}(\alpha,\beta_0)|=o_p(n_0^{1/3})\\ \max_{1\le j\le n_1}|\widehat{V}_{2j}(\alpha,\beta_0)|=o_p(n_0^{1/3})\\ \frac{1}{2n_0}\sum_{i=1}^{2n_0}|\widehat{V}_{1i}(\alpha,\beta_0)|^3=o_p(n_0^{1/3})\\ \frac{1}{n_1}\sum_{j=1}^{n_1}|\widehat{V}_{2j}(\alpha,\beta_0)|^3=o_p(n_0^{1/3}),\end{cases}$$

all hold uniformly in α.

Lemma 5. *For $\lambda_1=\lambda_1(\alpha)$ and $\lambda_2=\lambda_2(\alpha)$ satisfying (9) and (10), under conditions of Proposition 1, we have*

$$\lambda_l=O_p(n_0^{-1/3}),\quad l=1,2,$$

uniformly for $\{\alpha:|\alpha-\alpha_0|\le n_0^{-1/3}\}$.

Proof. From (9), we have

$$0=\left|\frac{1}{2n_0}\sum_{i=1}^{2n_0}\frac{\widehat{V}_{1i}(\alpha,\beta_0)}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)}\right|$$
$$\ge\frac{1}{2n_0}\left|\sum_{i=1}^{2n_0}\frac{\lambda_1\widehat{V}_{1i}^2(\alpha,\beta_0)}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)}\right|-\left|\frac{1}{2n_0}\sum_{i=1}^{2n_0}\widehat{V}_{1i}(\alpha,\beta_0)\right|$$
$$\ge\frac{|\lambda_1|\bar{U}_1^2(\alpha)}{1+|\lambda_1|\max_{1\le i\le 2n_0}|\widehat{V}_{1i}(\alpha,\beta_0)|}-U_1(\alpha),$$

combining this with Lemma 3 and (15), we have $\lambda_1=O_p(n_0^{-1/3})$. Similarly, we can show $\lambda_2=O_p(n_0^{-1/3})$. □

Proof of Proposition 1. By Lemma 5, we have

$$\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)=o_p(1),\qquad \lambda_2\widehat{V}_{2j}(\alpha,\beta_0)=o_p(1).$$

Since (9) is equal to

$$U_1(\alpha)-\lambda_1\bar{U}_1^2(\alpha)+\frac{1}{2n_0}\lambda_1^2\sum_{i=1}^{2n_0}\frac{\widehat{V}_{1i}^3(\alpha,\beta_0)}{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)}=0,$$

we have

$$(16)\qquad \lambda_1=[\bar{U}_1^2(\alpha)]^{-1}U_1(\alpha)+o_p(n_0^{-1/3}).$$

Similarly,

$$(17)\qquad \lambda_2=[\bar{U}_2^2(\alpha)]^{-1}U_2(\alpha)+o_p(n_0^{-1/3}).$$

Denote $l_1(\alpha,\beta_0)=2\sum_{i=1}^{2n_0}\log\{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)\}$, $l_2(\alpha,\beta_0)=2\sum_{j=1}^{n_1}\log\{1+\lambda_2\widehat{V}_{2j}(\alpha,\beta_0)\}$, and set $\alpha=\alpha_0+n_0^{-1/3}$. Applying Taylor expansion to $l_1(\alpha,\beta_0)$,

$$l_1(\alpha,\beta_0)=2\sum_{i=1}^{2n_0}\log\{1+\lambda_1\widehat{V}_{1i}(\alpha,\beta_0)\}$$
$$=2\lambda_1\sum_{i=1}^{2n_0}\widehat{V}_{1i}(\alpha,\beta_0)-\lambda_1^2\sum_{i=1}^{2n_0}\widehat{V}_{1i}^2(\alpha,\beta_0)+o_p(n_0^{1/3})$$

$$= 2n_0\{\bar U_1^2(\alpha)\}^{-1}U_1^2(\alpha) + o_p(n_0^{1/3})$$
$$= 2n_0\{\bar U_1^2(\alpha_0) + o_p(1)\}^{-1}$$
$$\times \{U_1(\alpha_0) + (U_1(\alpha^*)+1)(\alpha-\alpha_0)\}^2 + o_p(n_0^{1/3}).$$

By Lemma 3 and the fact that $U_1(\alpha) \to 0$ uniformly in $\{\alpha : |\alpha-\alpha_0| \le n_0^{-1/3}\}$, we obtain

$$l_1(\alpha,\beta_0) \ge Cn_0^{1/3}$$

with probability tending to one. On the other hand,

$$l_1(\alpha_0,\beta_0) = 2n_0\{\bar U_1^2(\alpha_0)\}^{-1}U_1^2(\alpha_0) + o_p(1) = O_p(1).$$

Thus, as $n_0 \to \infty$, with probability tending to one, it holds that $l_1(\alpha_0 + n_0^{-1/3},\beta_0) > l_1(\alpha_0,\beta_0)$. Similarly, we can show that $l_1(\alpha_0 - n_0^{-1/3},\beta_0) > l_1(\alpha_0,\beta_0)$. Also, we can prove $l_2(\alpha_0 \pm n_0^{-1/3},\beta_0) > l_2(\alpha_0,\beta_0)$ in the same manner.

Since $l_1(\alpha,\beta_0)$ and $l_2(\alpha,\beta_0)$ are continuous in $[\alpha_0 - n_0^{-1/3}, \alpha_0 + n_0^{-1/3}]$, $l(\alpha,\beta_0)$ attains its minimum in the interior of $[\alpha_0 - n_0^{-1/3}, \alpha_0 + n_0^{-1/3}]$, denoted by $\hat\alpha$. □

Proof of Theorem 1. Put $\hat\lambda_i = \lambda_i(\hat\alpha)$, $i = 1,2$. Then

$$Q_{jn_0n_1}(\hat\alpha,\hat\lambda_1,\hat\lambda_2) = 0, \quad j = 1,2,3.$$

By Taylor expansion, we have

(18)

$$\begin{aligned}0 &= Q_{jn_0n_1}(\alpha_0,0,0)\\ &\quad+ \frac{\partial}{\partial\lambda_1}Q_{jn_0n_1}(\alpha^*,\lambda_1^*,\lambda_2^*)\hat\lambda_1 + \frac{\partial}{\partial\lambda_2}Q_{jn_0n_1}(\alpha^*,\lambda_1^*,\lambda_2^*)\hat\lambda_2\\ &\quad+ \frac{\partial}{\partial\alpha}Q_{jn_0n_1}(\alpha^*,\lambda_1^*,\lambda_2^*)(\hat\alpha-\alpha_0),\end{aligned}$$

where α^* lies between $\hat\alpha$ and α_0, λ_l^* lies between $\hat\lambda_l$ and λ_l. Using Lemma 5, it can be checked that

$$\begin{aligned}&\lim_{n_0\to\infty}\frac{\partial}{\partial\lambda_1}Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2)\\ &\quad= \lim_{n_0\to\infty}\frac{1}{2n_0}\sum_{i=1}^{2n_0}\frac{-\widehat V_{1i}^2(\alpha,\beta_0)}{(1+\lambda_1\widehat V_{1i}(\alpha,\beta_0))^2}\\ &\quad= \lim_{n_0\to\infty}\frac{-1}{2n_0}\sum_{i=1}^{2n_0}\widehat V_{1i}^2(\alpha,\beta_0)\\ &\quad= -S_1^2,\\ &\lim_{n_0\to\infty}\frac{\partial}{\partial\lambda_2}Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2) = 0,\\ &\lim_{n_0\to\infty}\frac{\partial}{\partial\alpha}Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2)\\ &\quad= \lim_{n_0\to\infty}\frac{1}{2n_0}\sum_{i=1}^{2n_0}\frac{\widehat V_{1i}(\alpha,\beta_0)+1}{(1+\lambda_1\widehat V_{1i}(\alpha,\beta_0))^2}\\ &\quad= 1,\\ &\lim_{n_1\to\infty}\frac{\partial}{\partial\lambda_1}Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2) = 0,\\ &\lim_{n_1\to\infty}\frac{\partial}{\partial\lambda_2}Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2)\\ &\quad= \lim_{n_1\to\infty}\frac{1}{n_1}\sum_{j=1}^{n_1}\frac{-\widehat V_{2j}^2(\alpha,\beta_0)}{(1+\lambda_2\widehat V_{2j}(\alpha,\beta_0))^2}\\ &\quad= -S_2^2,\\ &\lim_{n_1\to\infty}\frac{\partial}{\partial\alpha}Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2)\\ &\quad= \lim_{n_1\to\infty}\frac{1}{n_1}\sum_{j=1}^{n_1}\frac{-\widehat V_{2j}(\alpha,\beta_0)-1}{(1+\lambda_2\widehat V_{2j}(\alpha,\beta_0))^2}\\ &\quad= -1,\\ &\lim_{n_0\to\infty}\frac{\partial}{\partial\lambda_1}Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2) = 1,\\ &\lim_{n_0\to\infty}\frac{\partial}{\partial\lambda_2}Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2) = -\rho,\\ &\lim_{n_0\to\infty}\frac{\partial}{\partial\alpha}Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2) = 0.\end{aligned}$$

All limits hold uniformly in $\{\alpha : |\alpha-\alpha_0| \le n_0^{-1/3}\}$. Therefore, solving the equation (18), we have

$$\begin{aligned}\begin{pmatrix}\hat\lambda_1\\ \hat\lambda_2\\ \hat\alpha-\alpha_0\end{pmatrix} &= -S_n^{-1}(\alpha^*,\lambda_1^*,\lambda_2^*)\begin{pmatrix}Q_{1n_0n_1}(\alpha_0,0,0)\\ Q_{2n_0n_1}(\alpha_0,0,0)\\ 0\end{pmatrix}\\ &= -S^{-1}\begin{pmatrix}Q_{1n_0n_1}(\alpha_0,0,0)\\ Q_{2n_0n_1}(\alpha_0,0,0)\\ 0\end{pmatrix} + o_p(1),\end{aligned}$$

where

$$\begin{aligned}&S_n(\alpha,\lambda_1,\lambda_2)\\ &\quad= \begin{pmatrix}\frac{\partial Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_1} & \frac{\partial Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_2} & \frac{\partial Q_{1n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\alpha}\\ \frac{\partial Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_1} & \frac{\partial Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_2} & \frac{\partial Q_{2n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\alpha}\\ \frac{\partial Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_1} & \frac{\partial Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\lambda_2} & \frac{\partial Q_{3n_0n_1}(\alpha,\lambda_1,\lambda_2)}{\partial\alpha}\end{pmatrix}\\ &\quad\xrightarrow{p} S := \begin{pmatrix}-S_1^2 & 0 & 1\\ 0 & -S_2^2 & -1\\ 1 & -\rho & 0\end{pmatrix}\end{aligned}$$

and thus

$$S^{-1} := \frac{1}{|S|}\begin{pmatrix}-\rho & -\rho & S_2^2\\ -1 & -1 & -S_1^2\\ S_2^2 & -\rho S_1^2 & S_1^2S_2^2\end{pmatrix},$$

where $|S| = S_1^2\rho + S_2^2$. So,

$$\begin{aligned}\hat\lambda_1 &= \frac{\rho}{|S|}\{Q_{1n_0n_1}(\alpha_0,0,0) + Q_{2n_0n_1}(\alpha_0,0,0)\} + o_p(1),\\ \hat\lambda_2 &= \frac{1}{|S|}\{Q_{1n_0n_1}(\alpha_0,0,0) + Q_{2n_0n_1}(\alpha_0,0,0)\} + o_p(1),\end{aligned}$$

$$\hat{\alpha} - \alpha_0 = \frac{-1}{|S|}\{S_2^2 Q_{1n_0n_1}(\alpha_0,0,0) - \rho S_1^2 Q_{2n_0n_1}(\alpha_0,0,0)\} + o_p(1).$$

The above gives that $\hat{\lambda}_1 = \rho\hat{\lambda}_2 + o_p(1)$. Furthermore,

$$\sqrt{n_1}\begin{pmatrix} Q_{1n_0n_1}(\alpha_0,0,0) \\ Q_{2n_0n_1}(\alpha_0,0,0)\end{pmatrix} \xrightarrow{d} N\left(\begin{pmatrix}0\\0\end{pmatrix}, \begin{pmatrix}\rho S_1^2 & 0 \\ 0 & S_2^2\end{pmatrix}\right),$$

which implies that

$$\sqrt{n_1}\hat{\lambda}_2 \xrightarrow{d} N(0, |S|^{-1}), \tag{19}$$

$$\begin{aligned} l(\beta_0) &= 2\left\{\sum_{i=1}^{2n_0}\log(1+\lambda_1\widehat{V}_{1i}(\hat{\alpha},\beta_0)) + \sum_{j=1}^{n_1}\log(1+\lambda_2\widehat{V}_{2j}(\hat{\alpha},\beta_0))\right\} \\ &= 2\sum_{i=1}^{2n_0}\lambda_1(\hat{\alpha})\widehat{V}_{1i}(\hat{\alpha},\beta_0) - \sum_{i=1}^{2n_0}\lambda_1^2(\hat{\alpha})\widehat{V}_{1i}^2(\hat{\alpha},\beta_0) + o_p(1) \\ &\quad + 2\sum_{j=1}^{n_1}\lambda_2(\hat{\alpha})\widehat{V}_{2j}(\hat{\alpha},\beta_0) - \sum_{j=1}^{n_1}\lambda_2^2(\hat{\alpha})\widehat{V}_{2j}^2(\hat{\alpha},\beta_0) + o_p(1) \\ &= 2n_0\hat{\lambda}_1^2\bar{U}_1^2(\hat{\alpha}) + n_1\hat{\lambda}_2^2\bar{U}_2^2(\hat{\alpha}) + o_p(1) \\ &= \{(\rho^{-1}+o(1))\rho^2\bar{U}_1^2(\alpha) + \bar{U}_2^2(\alpha)\}(\sqrt{n_1}\hat{\lambda}_2)^2 + o_p(1) \\ &= \{(\rho+o(1))S_1^2 + S_2^2\}(\sqrt{n_1}\hat{\lambda}_2)^2 + o_p(1) \\ &\xrightarrow{d} \chi_1^2. \end{aligned}$$

□

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