

Inference for Covariate Adjusted Regression via Varying Coefficient Models ¹

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We consider covariate adjusted regression (CAR), a regression method for situations where predictors and response are observed after being distorted by a multiplicative factor. The distorting factors are unknown functions of an observable covariate, where one specific distorting function is associated with each predictor or response. The dependence of both response and predictors on the same confounding covariate may alter the underlying regression relation between undistorted but unobserved predictors and response. We consider a class of highly flexible adjustment methods for parameter estimation in the underlying regression model, which is the model of interest. Asymptotic normality of the estimates is obtained by establishing a connection to varying coefficient models. These distribution results combined with proposed consistent estimates of the asymptotic variance are used for the construction of asymptotic confidence intervals for the regression coefficients. The proposed approach is illustrated with data on serum creatinine, and finite sample properties of the proposed procedures are investigated through a simulation study.

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Running Title: Inference for Adjusted Regression

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1. Introduction. For many statistical applications, a multiple linear regression model is a standard tool,

$$Y_{ni} = \gamma_0 + \sum_{r=1}^p \gamma_r X_{nri} + e_{ni}, \quad (1)$$

for data (X_{nri}, Y_{ni}) , $i = 1, \dots, n$, $r = 1, \dots, p$, where γ_0 and γ_r are unknown parameters, Y_{ni} is the response, X_{nri} is the r th predictor, and e_{ni} is the error term for the i th subject in the sample. An implicit assumption is that predictors and response are directly observable. However, in some situations both response and predictor variables may be distorted under the influence of a confounding variable. In this paper we consider a variant of (1), where one observes contaminated versions of predictors and response. Contamination of the variables in the regression model occurs through a multiplicative factor that is determined by the value of an unknown function of an observable covariate U . That is, instead of observing X_{nri} and Y_{ni} , one actually observes distorted variables \tilde{X}_{nri} and \tilde{Y}_{ni} ,

$$\tilde{X}_{nri} = \phi_r(U_{ni})X_{nri}, \quad r = 1, \dots, p, \quad \tilde{Y}_{ni} = \psi(U_{ni})Y_{ni}. \quad (2)$$

Here $\psi(\cdot)$ and $\phi_r(\cdot)$ are unknown smooth functions of the contaminating covariate U , and the available observations are $(U_{ni}, \tilde{X}_{nri}, \tilde{Y}_{ni})$.

An example where a model of this type is relevant are the creatinine data that are explored further in Section 5. Here serum creatinine levels are regressed on cholesterol level and serum albumin. Observed response and the two predictors are known to depend on body mass index, defined as Kg/m², which thus has a confounding effect on the regression relation. Therefore, we investigate the application of multiplicative confounding via model (2), where the confounding variable U is taken to be body mass index. ‘‘Normalization’’ by weight or body mass index is common in the analysis of medical data, and this refers to simply dividing the measured quantities by these confounding variables. This type of normalization implicitly assumes that the confounding is of multiplicative nature. The adjustment considered in this paper applies to a class of more general multiplicative confounding where the effects of the confounder are modelled by unknown distorting functions $\psi(\cdot)$ and $\phi_r(\cdot)$. This leads to flexible models that include

a large class of confounding mechanisms. Reasonable identifiability conditions for these functions are

$$E\{\psi(U)\} = 1, \quad E\{\phi_r(U)\} = 1, \quad r = 1, \dots, p, \quad (3)$$

corresponding to the assumption that the mean distorting effect vanishes. Additional basic assumptions are that the (X_r, U, e) are mutually independent for $r = 1, \dots, p$, and that observations made on different subjects are independent, with $E(e_{ni}) = 0$, and $\text{var}(e_{ni}) = \sigma^2$. The assumption that the underlying predictors, X_r , and response, Y , are independent of the contaminating variable U is an assumption defining the proposed contamination setting through defining these unobserved, underlying variables; and for that matter is not one that can be checked in practice. Thus, the question to be answered in practice is whether or not these independence conditions help define interpretable latent variables of interest from their observable counter parts. In our creatinine example, the latent variables are defined to be body mass index adjusted serum protein levels and cholesterol level, which are commonly used in medical studies.

The contamination of the predictor and response in a multiplicative fashion as given in (2) can alter the regression relation between the original response and predictors completely. It has also been shown for the case of simple linear regression, that standard adjustment methods such as nonparametric partial regression or partial regression cannot adjust for the multiplicative contamination [Şentürk and Müller (2003)]. Therefore, a modified parameter estimation procedure is necessary, which accounts for the multiplicative confounding effect of U . Such a procedure was proposed in Şentürk and Müller (2003), where consistent parameter estimation in model (1)-(3) was established. This estimation procedure relies on the fact that regressing \tilde{Y} on $\tilde{X}_1, \dots, \tilde{X}_p$ gives rise to a varying coefficient model. Furthermore, a main attraction of this estimation procedure is that under the identifiability conditions of vanishing mean distorting effects, it also works for the case of additive contamination, i.e. $\tilde{X}_{nri} = \phi_r(U_{ni}) + X_{nri}$, $\tilde{Y}_{ni} = \psi(U_{ni}) + Y_{ni}$, and for no contamination, i.e. $\phi_r(U_{ni}) = \psi(U_{ni}) = 1$ for $r = 1, \dots, p$. Thus, the proposed estimation procedure provides a flexible and general tool for adjustment, where the specific nature of the contamination of the variables or even its mere existence need not be

known.

The aim of this paper is to derive the asymptotic distribution of these parameter estimates, and to discuss applications to confidence intervals. We show that our proposed parameter estimates are asymptotically normal, and combining this result with consistent estimation of the asymptotic variance leads to asymptotic inference.

The paper is organized as follows. In Section 2 we describe the model in detail. In Section 3 issues of estimation are discussed and the results on asymptotic inference are presented. Consistent estimates for the asymptotic variance are derived in Section 4. Applications of the proposed method to creatinine data and simulation studies are in Section 5. The proofs of the main results are assembled in Section 6, followed by an Appendix with some additional technical conditions and auxiliary results.

2. Covariate adjustment via varying coefficient regression. Consider model (1)-(3). Writing $\tilde{X}_{ni} = (\tilde{X}_{n1i}, \dots, \tilde{X}_{npi})$, the regression of the observed response on the observed predictors leads to

$$\begin{aligned} E(\tilde{Y}_{ni} | \tilde{X}_{ni}^T, U_{ni}) &= E\{Y_{ni}\psi(U_{ni}) | \phi_1(U_{ni})X_{n1i}, \dots, \phi_p(U_{ni})X_{npi}, U_{ni}\} \\ &= \psi(U_{ni})E\{\gamma_0 + \sum \gamma_r X_{nri} + e_{ni} | \phi_1(U_{ni})X_{n1i}, \dots, \phi_p(U_{ni})X_{npi}, U_{ni}\}. \end{aligned}$$

Assuming that $E(e_{ni}) = 0$ and that (e, U, X_r) are mutually independent for $r = 1, \dots, p$, the model reduces to

$$\begin{aligned} E(\tilde{Y}_{ni} | \tilde{X}_{ni}^T, U_{ni}) &= \psi(U_{ni})\gamma_0 + \psi(U_{ni}) \sum \gamma_r \frac{\phi_r(U_{ni})X_{nri}}{\phi_r(U_{ni})} \\ &= \beta_0(U_{ni}) + \sum \beta_r(U_{ni})\tilde{X}_{nri}. \end{aligned} \tag{4}$$

Defining the functions

$$\beta_0(u) = \psi(u)\gamma_0, \quad \beta_r(u) = \gamma_r \frac{\psi(u)}{\phi_r(u)}, \tag{5}$$

this leads to

$$\tilde{Y}_{ni} = \beta_0(U_{ni}) + \sum \beta_r(U_{ni})\tilde{X}_{nri} + \epsilon(U_{ni}),$$

where $\epsilon(u) = \psi(u)e$.

We find that this is a multiple varying coefficient model, i.e., an extension of regression and generalized regression models where the coefficients are allowed to vary as a smooth function of a third variable [Hastie and Tibshirani (1993)]. A unique feature is that both response and predictors depend on the covariate U .

For varying coefficient models, Hoover, Rice, Wu and Yang (1998) have proposed smoothing methods based on local least squares and smoothing splines, and recent approaches include a componentwise kernel method [Wu and Chiang (2000)], a componentwise spline method [Chiang, Rice and Wu (2001)] and a method based on local maximum likelihood estimates [Cai, Fan and Li (2000)]. Wu and Yu (2002) provide a review of recent developments. We derive asymptotic distributions for an estimation method that is tailored to this special model.

3. Estimation and asymptotic distributions. The estimates of the regression coefficients γ_r will be obtained by targeting weighted averages of the smooth varying coefficient functions. Even though various smoothing methods have been proposed in the literature for the estimation of these smooth varying coefficient functions, we propose a smoothing method based on binning. The main reason for the use of the binning approach is its simplicity in targeting the desired weighted averages, rather than its performance on estimating the varying coefficient functions themselves. Nevertheless, the proposed binning approach has similarities with earlier developments for longitudinal data in Fan & Zhang (2000), who use the data collected at each fixed time point to fit a linear regression, obtaining the raw estimators for the smooth varying-coefficient functions.

Generalizing this idea to our independent and identically distributed data scheme, we assume that the covariate U is bounded below and above, $-\infty < a \leq U \leq b < \infty$ for real numbers $a < b$, and divide the interval $[a, b]$ into m equidistant intervals denoted by B_{n1}, \dots, B_{nm} , referred to as bins. Given m , the B_{nj} , $j = 1, \dots, m$ are fixed, but the number of U_{ni} 's falling into B_{nj} is random and is denoted by L_{nj} . For every U_{ni} falling in the j th bin, i.e., $U_{ni} \in B_{nj}$, the corresponding observed predictors are $\tilde{X}_{n1i}, \dots, \tilde{X}_{npi}$ and the response is \tilde{Y}_{ni} .

After binning the data, we fit a linear regression of \tilde{Y}_{ni} on $\tilde{X}_{n1i}, \dots, \tilde{X}_{npi}$ fusing the

data falling within each bin B_{nj} , $j = 1, \dots, m$. The least squares estimates of the resulting multiple regression for the data in the j th bin are denoted by $\hat{\beta}_{nj}^T = (\hat{\beta}_{n0j}, \dots, \hat{\beta}_{n pj})^T$. The estimators of γ_{n0} and γ_{nr} , for $r = 1, \dots, p$, are then obtained as weighted averages of the $\hat{\beta}_{nj}$'s, weighted according to the number of data L_{nj} in the j th bin,

$$\hat{\gamma}_{n0} = \sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{n0j} \quad (6)$$

and

$$\hat{\gamma}_{nr} = \frac{1}{\bar{X}_{nr}} \sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{nrj} \bar{X}'_{nrj}, \quad (7)$$

where $\bar{X}_{nr} = n^{-1} \sum_{i=1}^n \tilde{X}_{nri}$ and \bar{X}'_{nrj} is the average of the \tilde{X}_{nri} falling in B_{nj} , i.e., $L_{nj}^{-1} \sum_{i=1}^n \tilde{X}_{nri} \mathbf{1}_{\{U_{ni} \in B_{nj}\}}$ [Şentürk and Müller (2003)]. These estimates are motivated by $E\{\beta_0(U)\} = \gamma_0$ and $E\{\beta_r(U)\tilde{X}_r\} = \gamma_r E(\tilde{X}_r)$ (see (5) and (3)).

We present the asymptotic distribution of estimates $\hat{\gamma}_{n0}$ in (6), $\hat{\gamma}_{nr}$ in (7) for γ_0, γ_r in model (1), when the number of subjects n tends to infinity. As in typical smoothing applications, the number of bins $m = m(n)$ is required to satisfy $m \rightarrow \infty$, $n/(m \log n) \rightarrow \infty$ and $m/\sqrt{n} \rightarrow \infty$ as $n \rightarrow \infty$. We denote convergence in distribution by $\xrightarrow{\mathcal{D}}$ and convergence in probability by \xrightarrow{p} .

Theorem 1. *Under the technical conditions (C1)-(C7) in Section 6, on event E_n (defined in (12)) with $P(E_n) \rightarrow 1$ as $n \rightarrow \infty$,*

$$\sqrt{n}(\hat{\gamma}_{nr} - \gamma_r) \xrightarrow{\mathcal{D}} \mathbb{N}(0, \sigma_r^2), \quad 0 \leq r \leq p,$$

where

$$\begin{aligned} \sigma_0^2 &= \gamma_0^2 \text{var}\{\psi(U)\} + \sigma^2(\mathcal{X}^{-1})_{11} E\{\psi^2(U)\}, \\ \sigma_r^2 &= \frac{\gamma_r^2 [E(X_r^2) E\{\psi^2(U)\} - \{E(X_r)\}^2] + \sigma^2 \{E(X_r)\}^2 E\{\psi^2(U)\} (\mathcal{X}^{-1})_{rr}}{\{E(X_r)\}^2} \\ &\quad - \frac{2\gamma_r^2 [E\{\phi_r(U)\psi(U)\} E(X_r^2) - \{E(X_r)\}^2] + \gamma_r^2 \text{var}(\tilde{X}_r)}{\{E(X_r)\}^2}, \quad 1 \leq r \leq p, \end{aligned}$$

and

$$\mathcal{X} = \begin{bmatrix} 1 & E(X_1) & \dots & E(X_p) \\ E(X_1) & E(X_1^2) & \dots & E(X_1 X_p) \\ \vdots & & \ddots & \vdots \\ E(X_p) & E(X_1 X_p) & \dots & E(X_p^2) \end{bmatrix} \quad (8)$$

is assumed to be nonsingular, according to condition (C5) in Section 6.

4. Estimating the asymptotic variance. The observable data is of the form $(U_{ni}, \tilde{X}_{ni}^T, \tilde{Y}_{ni})$, $i = 1, \dots, n$, for a sample of size n , where $\tilde{X}_{ni} = (\tilde{X}_{n1i}, \dots, \tilde{X}_{npi})$ are the p -dimensional predictors. Correspondingly, the underlying unobservable predictors, responses and errors are $(X_{ni}^T, Y_{ni}, e_{ni})$, $i = 1, \dots, n$, where $X_{ni} = (X_{n1i}, \dots, X_{npi})$. Let $\{(U'_{nj}, \tilde{X}'_{nrjk}, \tilde{Y}'_{nj}, X'_{nrjk}, Y'_{nj}, e'_{nj}), k = 1, \dots, L_{nj}, r = 1, \dots, p\} = \{(U_{ni}, \tilde{X}_{nri}, \tilde{Y}_{ni}, X_{nri}, Y_{nri}, e_{nri}), i = 1, \dots, n, r = 1, \dots, p : U_{ni} \in B_{nj}\}$ denote the data for which $U_{ni} \in B_{nj}$, where we refer to $(U'_{nj}, \tilde{X}'_{nrjk}, \tilde{Y}'_{nj}, X'_{nrjk}, Y'_{nj}, e'_{nj})$ as the k th element in bin B_{nj} . Further let $(U_{nj}^T, \tilde{X}'_{nj}, \tilde{Y}'_{nj}, X'_{nj}, Y'_{nj}, e_{nj}^T)$ be the data matrix belonging to the j th bin, where $U'_{nj} = (U'_{nj1}, \dots, U'_{njL_{nj}})$, $\tilde{Y}'_{nj} = (\tilde{Y}'_{nj1}, \dots, \tilde{Y}'_{njL_{nj}})$, $Y'_{nj} = (Y'_{nj1}, \dots, Y'_{njL_{nj}})$, $e'_{nj} = (e'_{nj1}, \dots, e'_{njL_{nj}})$ and $\tilde{X}'_{nj} = (1, \tilde{X}'_{n1jk}, \dots, \tilde{X}'_{npijk})$, $X'_{nj} = (1, X'_{n1jk}, \dots, X'_{npijk})$ for $k = 1, \dots, L_{nj}$ contain p components of the k th element in bin j , and

$$\tilde{X}'_{nj} = (\tilde{X}'_{nj1}, \dots, \tilde{X}'_{njL_{nj}})_{L_{nj} \times (p+1)}^T, \quad X'_{nj} = (X'_{nj1}, \dots, X'_{njL_{nj}})_{L_{nj} \times (p+1)}^T.$$

Then we can express the least squares estimates of the multiple regression of the observable data falling in the j th bin B_{nj} as

$$\hat{\beta}_{nj}^T = (\hat{\beta}_{n0j}, \dots, \hat{\beta}_{npij})^T = (\tilde{X}'_{nj}{}^T \tilde{X}'_{nj})^{-1} \tilde{X}'_{nj}{}^T \tilde{Y}'_{nj}, \quad (9)$$

leading to the parameter estimates $\hat{\gamma}_{n0}$ and $\hat{\gamma}_{nr}$ given in (6) and (7), respectively, where $\tilde{X}_{nr} = n^{-1} \sum_{i=1}^n \tilde{X}_{nri}$ and $\tilde{X}'_{nrj} = L_{nj}^{-1} \sum_{k=1}^{L_{nj}} \tilde{X}'_{nrjk}$.

Let $\tilde{\gamma}_{nj}$ be the least squares estimates of the multiple regression of the unobservable data falling into B_{nj} , i.e.,

$$\tilde{\gamma}_{nj}^T = (\tilde{\gamma}_{n0j}, \dots, \tilde{\gamma}_{npij})^T = (X'_{nj}{}^T X'_{nj})^{-1} X'_{nj}{}^T Y'_{nj}. \quad (10)$$

This quantity is not estimable, but will be used in the proof of the main results.

For the estimates given in (6) and (7) to be well defined, the least squares estimate $\hat{\beta}_{nj}$ must exist for each bin B_{nj} . This requires that the inverse of $\tilde{X}'_{nj}{}^T \tilde{X}'_{nj}$ is well defined, i.e. $\det(\tilde{X}'_{nj}{}^T \tilde{X}'_{nj}) \neq 0$. Correspondingly, $\tilde{\gamma}_{nj}$ will exist under the condition that $\det(X'_{nj}{}^T X'_{nj}) \neq 0$.

0. Define the events

$$\begin{aligned}\tilde{A}_n &= \{\omega \in \Omega : \inf_j |\det(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')| > \zeta \text{ and } \min_j L_{nj} > p\}, \\ A_n &= \{\omega \in \Omega : \inf_j |\det(L_{nj}^{-1} X_{nj}'^T X_{nj}')| > \zeta \text{ and } \min_j L_{nj} > p\},\end{aligned}\quad (11)$$

where $\zeta = \min\{\rho/2, [\inf_j(\phi_1^2(U_{nj}^*), \dots, \phi_p^2(U_{nj}^*))]^p \rho/2\}$, ρ is as defined in (C5), $U_{nj}^* = L_{nj}^{-1} \sum_{k=1}^{L_{nj}} U_{nj,k}'$ is the average of the U 's in B_{nj} , and (Ω, \mathcal{F}, P) is the underlying probability space. On event \tilde{A}_n , $\hat{\gamma}_{n0}$ and $\hat{\gamma}_{nr}$ given in (6) and (7), and on event A_n , $\tilde{\gamma}_{nj}$ given in (10) are well defined, respectively. Event E_n in Theorems 1 and 2 is defined to be the intersection of A_n and \tilde{A}_n , i.e.,

$$E_n = A \cap \tilde{A}_n. \quad (12)$$

It is shown in Appendix A.3 that $P(E_n) \rightarrow 1$ as $n \rightarrow \infty$.

Theorem 2. *Under the technical conditions (C1)-(C7) in Section 6, on event E_n (defined in (12)) with $P(E_n) \rightarrow 1$ as $n \rightarrow \infty$,*

$$\hat{\sigma}_{nr}^2 \xrightarrow{p} \sigma_r^2, \quad 0 \leq r \leq p,$$

where

$$\begin{aligned}\hat{\sigma}_{n0}^2 &= \left(\sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{n0j}^2 - \hat{\gamma}_{n0}^2 \right) + \left\{ \frac{1}{n} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} (\tilde{Y}_{nj,k}' - \hat{\beta}_{n0j} - \hat{\beta}_{n1j} \tilde{X}_{n1jk}' - \dots - \hat{\beta}_{npj} \tilde{X}_{npj,k}')^2 \right\} \\ &\quad \left\{ \sum_{j=1}^m \frac{L_{nj}}{n} (L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')^{-1}_{11} \right\}, \\ \hat{\sigma}_{nr}^2 &= \left[\frac{1}{n} \sum_{j=1}^m \hat{\beta}_{nrj}^2 \sum_{k=1}^{L_{nj}} \tilde{X}_{nrjk}^{\prime 2} + \hat{\gamma}_{nr}^2 \tilde{X}_{nr}^2 - 2 \frac{\hat{\gamma}_{nr}}{n} \sum_{j=1}^m \hat{\beta}_{nrj} \sum_{k=1}^{L_{nj}} \tilde{X}_{nrjk}^{\prime 2} + \hat{\gamma}_{nr}^2 s_{\tilde{X}_r}^2 \right. \\ &\quad \left. + \left\{ \frac{1}{n} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} (\tilde{Y}_{nj,k}' - \hat{\beta}_{n0j} - \hat{\beta}_{n1j} \tilde{X}_{n1jk}' - \dots - \hat{\beta}_{npj} \tilde{X}_{npj,k}')^2 \right\} \right. \\ &\quad \left. \left\{ \sum_{j=1}^m \frac{L_{nj}}{n} \tilde{X}_{nrj}^2 (L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')^{-1}_{rr} \right\} \right] / \tilde{X}_{nr}^2, \quad 1 \leq r \leq p,\end{aligned}$$

and $s_{\tilde{X}_r}^2 = (n-1)^{-1} \sum_{i=1}^n (\tilde{X}_{nri} - \tilde{X}_{nr})^2$.

Remark. These proposed variance estimates are motivated by the identifiability conditions, the definition of the smooth varying coefficients functions given in (5), Lemma 3

and Lemma 4 (a.). Using the consistency of $\hat{\beta}_{nrj}$ for the value of the function β_r at the mid point of the j th bin and the definitions of \tilde{Y}'_{nj} and \tilde{X}'_{nrjk} , we target the quantities $\sigma^2 E\{\psi(U)\}$, $\gamma_0^2 E\{\psi^2(U)\}$, $\gamma_r^2 E(X_r^2)E\{\psi^2(U)\}$ and $\gamma_r^2 E\{\phi_r(U)\psi(U)\}E(X_r^2)$ with the estimators $n^{-1} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} (\tilde{Y}'_{nj} - \hat{\beta}_{n0j} - \hat{\beta}_{n1j} \tilde{X}'_{n1jk} - \dots - \hat{\beta}_{n pj} \tilde{X}'_{n pj k})^2$, $\sum_{j=1}^m n^{-1} L_{nj} \hat{\beta}_{n0j}^2$, $n^{-1} \sum_{j=1}^m \hat{\beta}_{nrj}^2 \sum_{k=1}^{L_{nj}} \tilde{X}'_{nrjk}{}^2$ and $n^{-1} \hat{\gamma}_{nr} \sum_{j=1}^m \hat{\beta}_{nrj} \sum_{k=1}^{L_{nj}} \tilde{X}'_{nrjk}{}^2$, respectively. Furthermore, relying mainly on Lemma 3 and Lemma 4 (a.), we target $(\mathcal{X}^{-1})_{11}$ and $\{E(X_r)\}^2 (\mathcal{X}^{-1})_{rr}$ with $\sum_{j=1}^m n^{-1} L_{nj} (L_{nj}^{-1} \tilde{X}'_{nj}{}^T \tilde{X}'_{nj})_{11}^{-1}$ and $\sum_{j=1}^m n^{-1} L_{nj} \tilde{X}'_{nrj}{}^2 (L_{nj}^{-1} \tilde{X}'_{nj}{}^T \tilde{X}'_{nj})_{rr}^{-1}$, respectively.

5. Applications and Monte Carlo study. Under the technical conditions (C1)-(C7) in Section 6,

$$\frac{\sqrt{n}}{\sigma_r} (\hat{\gamma}_{nr} - \gamma_r) \xrightarrow{\mathcal{D}} \mathbb{N}(0, 1), \quad 0 \leq r \leq p, \quad \text{as } n \rightarrow \infty. \quad (13)$$

Using the consistent estimate $\hat{\sigma}_{nr}^2$ of σ_r^2 proposed in Theorem 2, it follows from (13) and Slutsky's theorem that

$$\frac{\sqrt{n}}{\hat{\sigma}_{nr}} (\hat{\gamma}_{nr} - \gamma_r) \xrightarrow{\mathcal{D}} \mathbb{N}(0, 1), \quad 0 \leq r \leq p,$$

so that an approximate $(1 - \alpha)$ asymptotic confidence interval for γ_r has the endpoints

$$\hat{\gamma}_{nr} \pm z_{\alpha/2} \frac{\hat{\sigma}_{nr}}{\sqrt{n}}. \quad (14)$$

Here $z_{\alpha/2}$ is the $(1 - \alpha/2)$ th quantile of the standard Gaussian distribution.

5.1. Application to Creatinine Data. An observational study in which various laboratory and patient data were analyzed for patients with end-stage renal disease is described in Kaysen et al. (2004). To illustrate our methods, we use a subset of these data. Variables include serum creatinine level (*CRT*), cholesterol level (*CH*), serum albumin level (*ALB*) and body mass index (*BMI*), measured for $n = 508$ subjects. Creatinine is a protein produced by muscle and released into blood. Since the amount produced is relatively stable, the creatinine level in the serum is determined by the rate it is removed, and is therefore an important indicator of renal function. We analyze the dependency of serum creatinine (response) on cholesterol level and serum albumin (predictors). An unadjusted

approach would be to fit the multiple regression model $CRT = \gamma_0 + \gamma_1 CH + \gamma_2 ALB + e$, where e is an error term, usually by least squares. Body mass index (BMI) is defined as weight/height² and is known to affect both the response and the predictors. This provides the motivation to adjust for this influence by means of the CAR model (4), (5), using body mass index as the confounder U .

The parameters γ_0 , γ_1 and γ_2 were estimated by the CAR algorithm and the results were compared to the estimators obtained from the least squares regression of the observed CRT on observed CH and ALB . The estimators and the approximate 95% asymptotic confidence intervals for the regression parameters obtained through both methods are displayed in Table 1. The approximate confidence intervals for CAR estimates were obtained as proposed in (14). The scatter-plots of the raw estimates $(\hat{\beta}_{nr1}, \dots, \hat{\beta}_{nrp})$ (9) vs. midpoints of the bins (B_{n1}, \dots, B_{nm}) are shown in Figure 1 for $r = 0, 1, 2$.

The implementation of the binning algorithm allows for merging of sparsely populated bins. Bin widths were chosen such that there are at least $(p + 1)$ points, enough to fit the linear regression with $(p - 1)$ predictors in each bin. If there were bins with less than $(p + 1)$ elements, such bins were merged with neighboring bins. For this example with $n = 508$, the average number of points per bin was 14, yielding a total of 34 bins after merging.

For least squares regression, CH was not found significant at the usual 5% level, while ALB was found to be significant. When applying the CAR method, CH and ALB were both significant. As BMI increases, the slope parameter of serum albumin level increases exponentially, while the negative slope parameter of cholesterol level declines slightly. Adjusting for different BMI levels across patients, both serum albumin level and cholesterol level seem to play a significant role for the serum creatinine level. The effects of BMI are thus masking the true overall negative effect that CH has on CRT in the unadjusted regression equation.

5.2. *Monte Carlo simulation.* The confounding covariate U was simulated from

Uniform(2, 6). The underlying unobserved multiple regression model was

$$Y = 4 - X_1 + 0.3X_2 + 3X_3 + e, \quad (15)$$

where $X_1 \sim \mathcal{N}(1.5, 0.7)$, $X_2 \sim \mathcal{N}(1, 1.2)$, $X_3 \sim \mathcal{N}(0.5, 1)$, and $e \sim \mathcal{N}(0, 0.3)$. The distortion functions were chosen as $\psi(U) = (U+3)/7$, $\phi_1(U) = (U+1)^2/26.3333$, $\phi_2(U) = (U+10)/14$ and $\phi_3(U) = (U+2)^2/37.3333$, satisfying the identifiability conditions. We conducted 1000 Monte Carlo runs with sample sizes 100, 400 and 1600. For each run approximate 95% asymptotic confidence intervals were formed for the regression parameters by plugging in the estimates $\hat{\sigma}_{nr}^2$, $r = 0, \dots, p$, given in Theorem 2, into (14). The estimated coverage fractions and mean interval lengths for these confidence intervals are given in Table 2. The estimated non-coverage fractions are seen to get very close to the target value 0.05, as sample size increases, and the estimated interval lengths are sharply decreasing.

We have also carried out simulations to study the effects of different choices of m , the total number of bins, on the mean square error of the CAR estimates. Under the rate conditions on m given in Section 3, the estimates are found to be sufficiently robust regarding different choices of m .

6. Proofs of the main results. While the main steps in the proofs of the two theorems are given here, the auxiliary results for these proofs are deferred to the Appendix, where they are listed as lemmas 1 to 4. We introduce some technical conditions:

(C1) The covariate U is bounded below and above, $-\infty < a \leq U \leq b < \infty$ for real numbers $a < b$. The density $f(u)$ of U satisfies $\inf_{a \leq u \leq b} f(u) > c_1 > 0$, $\sup_{a \leq u \leq b} f(u) < c_2 < \infty$ for real c_1, c_2 , and is uniformly Lipschitz continuous, i.e., there exists a real number M such that $\sup_{a \leq u \leq b} |f(u+c) - f(u)| \leq M|c|$ for any real number c .

(C2) The variables (e, U, X_r) are mutually independent for $r = 1, \dots, p$.

(C3) For the predictors, $\sup_{1 \leq i \leq n, 1 \leq r \leq p} |X_{nri}| \leq B$ for some bound $B \in \mathbb{R}$.

(C4) Contamination functions $\psi(\cdot)$ and $\phi_r(\cdot)$, $1 \leq r \leq p$, are twice continuously differentiable, satisfying

$$E\psi(U) = 1, \quad E\phi_r(U) = 1, \quad \phi_r(\cdot) > 0 \quad 1 \leq r \leq p.$$

(C5) As $n \rightarrow \infty$, $\frac{1}{n}X^T X \xrightarrow{p} \mathcal{X}$, where \mathcal{X} , the limiting $(p+1) \times (p+1)$ -matrix, is nonsingular, i.e. $\rho = |\det(\mathcal{X})| > 0$.

These are mild conditions that are satisfied in most practical situations. Bounded covariates are standard in asymptotic theory for least squares regression, as are conditions (C2) and (C5) [see Lai, Robbins and Wei (1979)]. The identifiability conditions stated in (C4) are equivalent to

$$E(\tilde{Y}|X) = E(Y|X), \quad E(\tilde{X}_r|X_r) = X_r.$$

This means that the confounding of Y by U does not change the mean regression function. Some further technical conditions will be introduced in Appendix A.1; these are required to prove the auxiliary Lemmas in the Appendix.

For two matrices of the same dimension, let $A \square B$ denote the Hadamard product, where $A \square B$ is also of the same dimension with (i, j) th element equal to the product of the (i, j) th elements of A and B .

Proof of Theorem 1. By Lemma 4 (b.) and properties (b.), (c.), (e.), (f.) given in Appendix A.3, it holds that

$$\sup_j |(L_{nj}^{-1} \tilde{X}_{nj}^{\prime T} \tilde{Y}_{nj}') - \{\Delta \square (L_{nj}^{-1} X_{nj}^{\prime T} Y_{nj}')\}| = O_p(m^{-1}) \mathbf{1}_{(p+1) \times 1}, \quad (16)$$

where $(L_{nj}^{-1} \tilde{X}_{nj}^{\prime T} \tilde{Y}_{nj}') = (L_{nj}^{-1} \sum_k \tilde{Y}'_{nj k}, L_{nj}^{-1} \sum_k \tilde{Y}'_{nj k} \tilde{X}'_{n1jk}, \dots, L_{nj}^{-1} \sum_k \tilde{Y}'_{nj k} \tilde{X}'_{npj k})^T$,

$(L_{nj}^{-1} X_{nj}^{\prime T} Y_{nj}') = (L_{nj}^{-1} \sum_k Y'_{nj k}, L_{nj}^{-1} \sum_k Y'_{nj k} X'_{n1jk}, \dots, L_{nj}^{-1} \sum_k Y'_{nj k} X'_{npj k})^T$,

$\Delta = \{\psi(U_{nj}^*), \psi(U_{nj}^*)\phi_1(U_{nj}^*), \dots, \psi(U_{nj}^*)\phi_p(U_{nj}^*)\}^T$, and $\mathbf{1}_{(p+1) \times 1}$ denotes a $(p+1) \times 1$ vector of ones. Under event E_n , Lemma 3 and (16) imply that

$$\sup_j \left| \begin{array}{l} \hat{\beta}_{n0j} - \psi(U_{nj}^*) \tilde{\gamma}_{n0j} \\ \hat{\beta}_{n1j} - \{\psi(U_{nj}^*)/\phi_1(U_{nj}^*)\} \tilde{\gamma}_{n1j} \\ \vdots \\ \hat{\beta}_{npj} - \{\psi(U_{nj}^*)/\phi_p(U_{nj}^*)\} \tilde{\gamma}_{npj} \end{array} \right| = O_p(m^{-1}) \mathbf{1}_{(p+1) \times 1}, \quad (17)$$

where $\tilde{\gamma}_{nj}$ is as defined in (10). First consider the case $r = 0$. Using (17),

$$\begin{aligned} \sqrt{n}(\hat{\gamma}_{n0} - \gamma_0) &= \sqrt{n} \left(\sum_j^m \frac{L_{nj}}{n} \hat{\beta}_{n0j} - \gamma_0 \right) = \sum_j^m \frac{L_{nj}}{\sqrt{n}} \psi(U_{nj}^*) \tilde{\gamma}_{n0j} - \sqrt{n} \gamma_0 + O_p \left(\frac{\sqrt{n}}{m} \right) \\ &= \sum_j^m \frac{L_{nj}}{\sqrt{n}} \psi(U_{nj}^*) [\gamma_0 + \{(X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT} e'_{nj}\}_1] - \sqrt{n} \gamma_0 + O_p \left(\frac{\sqrt{n}}{m} \right). \end{aligned}$$

By property (b.), Lemma 4 (a.), (b.) and substituting $L_{nj}^{-1} \sum_k \{L_{nj}^{-1} X_{nj}^{rT} X'_{nj}\}^{-1} X_{nj}^{rT}\}_{1k} e'_{nj}$ for $\{(X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT} e'_{nj}\}_1$, $\sqrt{n}(\hat{\gamma}_{n0} - \gamma_0)$ further simplifies to

$$\sum_{j=1}^m \sum_{k=1}^{L_{nj}} \left[\frac{\gamma_0 \psi(U'_{nj})}{\sqrt{n}} + \frac{\psi(U'_{nj}) e'_{nj}}{\sqrt{n}} \{(L_{nj}^{-1} X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT}\}_{1k} \right] - \sqrt{n} \gamma_0 + O_p \left(\frac{\sqrt{n}}{m} \right). \quad (18)$$

Since the above sum is over all bins indexed by j , and over all points within the bins indexed by k , it is equal to the sum over all data points indexed by i , summed up in a random order. We introduce notation where $X'_{nj(i)}$ refers to the matrix X'_{nj} and $L_{nj(i)}$ refers to the number of points in the j th bin such that $U_{ni} \in B_{nj}$, and $\{(L_{nj(i)}^{-1} X_{nj(i)}^{rT} X'_{nj(i)})^{-1} X_{nj(i)}^{rT}\}_{rk(i)}$ is the (r, k) th element of the matrix $\{(L_{nj}^{-1} X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT}\}$ for $1 \leq r \leq p$, where $U_{ni} = U'_{nj}$ is the k th element in the ordered sample $(U'_{nj1}, \dots, U'_{njL_{nj}}) \in B_{nj}$. Thus (18) is equal to

$$\sum_{\substack{i=1 \\ j,k}}^n \left[\frac{\gamma_0 \psi(U_{ni})}{\sqrt{n}} + \frac{\psi(U_{ni}) e_{ni}}{\sqrt{n}} \{(L_{nj(i)}^{-1} X_{nj(i)}^{rT} X'_{nj(i)})^{-1} X_{nj(i)}^{rT}\}_{1k(i)} - \frac{\gamma_0}{\sqrt{n}} \right] + O_p \left(\frac{\sqrt{n}}{m} \right). \quad (19)$$

The term $\sqrt{n}(\hat{\gamma}_{n0} - \gamma_0)$ is asymptotically equivalent to

$$S_{n0t} = \sum_{\substack{i=1 \\ j,k}}^t \left[\frac{\gamma_0 \psi(U_{ni})}{\sqrt{n}} + \frac{\psi(U_{ni}) e_{ni}}{\sqrt{n}} \{(L_{nj(i)}^{-1} X_{nj(i)}^{rT} X'_{nj(i)})^{-1} X_{nj(i)}^{rT}\}_{1k(i)} - \frac{\gamma_0}{\sqrt{n}} \right] = \sum_{i=1}^t Z_{n0i},$$

since $m/\sqrt{n} \rightarrow \infty$ as $n \rightarrow \infty$ makes the term $O_p(\sqrt{n}/m)$ negligible.

Let F_{n0t} be the σ -field generated by $\{e_{n1}, \dots, e_{nt}, U_{n1}, \dots, U_{nt}, L_{nj(1)}, \dots, L_{nj(t)}, X'_{nj(1)}, \dots, X'_{nj(t)}\}$. Then $\{S_{n0t} = \sum_{i=1}^t Z_{n0i}, F_{n0t}, 1 \leq t \leq n\}$ is a mean zero martingale for $n \geq 1$; since $E(S_{n0t}) = 0$, $E(S_{n0,t+1}|F_{n0t}) = S_{n0t}$, and S_{n0t} is adapted to F_{n0t} . Since the σ -fields are nested, that is, $F_{n0t} \subseteq F_{n0,t+1}$ for all $t \leq n$, using Lemma 1, $S_{n0n} \rightarrow \mathbb{N}(0, \sigma_0^2)$ in distribution [McLeish (1974), Theorem 2.3 and subsequent discussion], and Theorem 1 follows for $r = 0$.

Next we show

$$\sqrt{n} \begin{pmatrix} \sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{nrj} \bar{X}'_{nrj} & - \gamma_r E(X_r) \\ \sum_{j=1}^m \frac{L_{nj}}{n} \bar{X}'_{nrj} & - E(X_r) \end{pmatrix} \xrightarrow{\mathcal{D}} \mathbb{N}_2(\mathbf{0}, \Sigma_r). \quad (20)$$

The asymptotic normality of $\sqrt{n}(\hat{\gamma}_{nr} - \gamma_r)$ for $r = 1, \dots, p$ will follow from this with a simple application of δ -method, since $\hat{\gamma}_{nr} = (\sum_{j=1}^m L_{nj} n^{-1} \hat{\beta}_{nrj} \bar{X}'_{nrj}) / (\sum_{j=1}^m L_{nj} n^{-1} \bar{X}'_{nrj})$ as defined in (7). By the Cramer Wald device it is enough to show the asymptotic normality of $\sqrt{n}[a\{\sum_{j=1}^m L_{nj} n^{-1} \hat{\beta}_{nrj} \bar{X}'_{nrj} - \gamma_r E(X_r)\} + b\{\sum_{j=1}^m L_{nj} n^{-1} \bar{X}'_{nrj} - E(X_r)\}]$ for real a, b , and (20) will follow.

Using (17), properties (b.), (c.), Lemma 4 (a.), (b.) and substituting $L_{nj}^{-1} \sum_k \{L_{nj}^{-1} X_{nj}^{rT} X'_{nj}\}^{-1} X_{nj}^{rT} e'_{nj}$ for $\{(X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT} e'_{nj}\}_r$, we have

$$\begin{aligned} \sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{nrj} \bar{X}'_{nrj} &= \sum_{j=1}^m \frac{L_{nj}}{n} \psi(U_{nj}^*) \bar{X}'_{nrj} [\gamma_r + \{(X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT} e'_{nj}\}_r] + O_p(m^{-1}) \\ &= \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \left[\frac{\gamma_r}{n} \psi(U_{nj}) X'_{nrjk} + \frac{\bar{X}'_{nrj}}{n} \psi(U_{nj}) e'_{nj} \{(L_{nj}^{-1} X_{nj}^{rT} X'_{nj})^{-1} X_{nj}^{rT}\}_{rk} \right] + O_p(m^{-1}), \end{aligned}$$

and

$$\sum_{j=1}^m \frac{L_{nj}}{n} \bar{X}'_{nrj} = \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \frac{1}{n} \phi_r(U_{nj}) X'_{nrjk} + O_p(m^{-1}).$$

Thus using the same notation as in (19), it holds that

$$\begin{aligned} &\sqrt{n} \left[a \left\{ \sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{nrj} \bar{X}'_{nrj} - \gamma_r E(X_r) \right\} + b \left\{ \sum_{j=1}^m \frac{L_{nj}}{n} \bar{X}'_{nrj} - E(X_r) \right\} \right] \\ &= \sum_{\substack{i=1 \\ j,k}}^n \left[a \frac{\gamma_r}{\sqrt{n}} \psi(U_{ni}) X_{nri} + a \frac{\bar{X}'_{nrj(i)}}{\sqrt{n}} \psi(U_{ni}) e_{ni} \{(L_{nj(i)}^{-1} X_{nj(i)}^{rT} X'_{nj(i)})^{-1} X_{nj(i)}^{rT}\}_{rk(i)} \right. \\ &\quad \left. - a \frac{\gamma_r}{\sqrt{n}} E(X_r) + \frac{b}{\sqrt{n}} \phi_r(U_{ni}) X_{nri} - b \frac{E(X_r)}{\sqrt{n}} \right] + O_p\left(\frac{\sqrt{n}}{m}\right), \end{aligned}$$

where $\bar{X}'_{nrj(i)} = L_{nj(i)}^{-1} \sum_{k=1}^{L_{nj(i)}} X'_{nrj(i)k}$. Since $O_p(\sqrt{n}/m)$ is asymptotically negligible, the above term is asymptotically equivalent to

$$S_{nrt} = \sum_{\substack{i=1 \\ j,k}}^n \left[a \frac{\gamma_r}{\sqrt{n}} \psi(U_{ni}) X_{nri} + a \frac{\bar{X}'_{nrj(i)}}{\sqrt{n}} \psi(U_{ni}) e_{ni} \{(L_{nj(i)}^{-1} X_{nj(i)}^{rT} X'_{nj(i)})^{-1} X_{nj(i)}^{rT}\}_{rk(i)} \right]$$

$$-a \frac{\gamma_r}{\sqrt{n}} E(X_r) + \frac{b}{\sqrt{n}} \phi_r(U_{ni}) X_{nri} - b \frac{E(X_r)}{\sqrt{n}} \Big] = \sum_{i=1}^t Z_{nri}.$$

Let F_{nrt} be the σ -field generated by $\{e_{n1}, \dots, e_{nt}, U_{n1}, \dots, U_{nt}, L_{nj(1)}, \dots, L_{nj(t)}, X'_{nj(1)}, \dots, X'_{nj(t)}\}$. Then it is easy to check that $\{S_{nrt} = \sum_{i=1}^t Z_{nri}, F_{nrt}, 1 \leq t \leq n\}$ is a mean zero martingale for $n \geq 1$. Since the σ -fields are nested, that is, $F_{nrt} \subseteq F_{nr,t+1}$ for all $t \leq n$, using Lemma 2, $S_{nrn} \xrightarrow{\mathcal{D}} \mathbb{N}(0, (a, b)\Sigma_r(a, b)^T)$. Thus, it also follows by a simple application of the δ -method that $\sqrt{n}(\hat{\gamma}_{nr} - \gamma_r) \xrightarrow{p} \mathbb{N}(0, \sigma_r^2)$ for $r = 1, \dots, p$, where σ_r^2 is as defined in Theorem 1.

Proof of Theorem 2. Using Lemma 4 (a.) and (b.), it holds on event A_n that

$$\sup_j |\tilde{\gamma}_{nj} - \underline{\gamma}| = o_p(1) \mathbf{1}_{(p+1) \times 1}, \quad (21)$$

where $\underline{\gamma} = (\gamma_0, \gamma_1, \dots, \gamma_p)^T$. Using (21) and (17),

$$\sup_j \left| \begin{array}{l} \hat{\beta}_{n0j} - \psi(U_{nj}^*) \gamma_0 \\ \hat{\beta}_{n1j} - \{\psi(U_{nj}^*) / \phi_1(U_{nj}^*)\} \gamma_1 \\ \vdots \\ \hat{\beta}_{npj} - \{\psi(U_{nj}^*) / \phi_p(U_{nj}^*)\} \gamma_p \end{array} \right| = o_p(1) \mathbf{1}_{(p+1) \times 1}. \quad (22)$$

By (22), properties (b.), (c.), (d.), boundedness considerations and the law of large numbers,

$$\sum_{j=1}^m \frac{L_{nj}}{n} \hat{\beta}_{n0j}^2 = \gamma_0^2 \sum_{j=1}^m \frac{L_{nj}}{n} \{\psi^2(U_{nj}^*) + o_p(1)\} = \frac{\gamma_0^2}{n} \sum_{i=1}^n \psi^2(U_{ni}) + o_p(1) = \gamma_0^2 E\{\psi^2(U)\} + o_p(1),$$

$$\begin{aligned} & \frac{1}{n} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} (\tilde{Y}'_{nj k} - \hat{\beta}_{n0j} - \hat{\beta}_{n1j} \tilde{X}'_{n1jk} - \dots - \hat{\beta}_{npj} \tilde{X}'_{npj k})^2 \\ &= \frac{1}{n} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \left\{ \psi(U_{nj}^*) e'_{nj k} + \delta_{n0jk} Y'_{nj k} - \gamma_1 \frac{\psi(U_{nj}^*)}{\phi_1(U_{nj}^*)} \delta_{n1jk} X'_{n1jk} - \dots \right. \\ & \left. - \gamma_p \frac{\psi(U_{nj}^*)}{\phi_p(U_{nj}^*)} \delta_{npj k} X'_{npj k} + o_p(1) \right\}^2 \end{aligned}$$

$$\begin{aligned}
&= \frac{1}{n} \sum_{i=1}^n \psi(U_{ni}^2) e_{ni}^2 + o_p(1) = \sigma^2 E\{\psi^2(U)\} + o_p(1), \\
&\frac{1}{n} \sum_{j=1}^m \hat{\beta}_{nrj}^2 \sum_{k=1}^{L_{nj}} \tilde{X}_{nrjk}^{\prime 2} = \frac{\gamma_r^2}{n} \sum_{j=1}^m \psi^2(U_{nj}^*) \sum_{k=1}^{L_{nj}} X_{nrjk}^{\prime 2} + o_p(1) \\
&= \frac{\gamma_r^2}{n} \sum_{i=1}^n \psi^2(U_{ni}) X_{nri}^2 + o_p(1) = \gamma_r^2 E\{\psi^2(U)\} E(X_r^2) + o_p(1),
\end{aligned}$$

and

$$\begin{aligned}
&\frac{1}{n} \sum_{j=1}^m \hat{\beta}_{nrj} \sum_{k=1}^{L_{nj}} \tilde{X}_{nrjk}^{\prime 2} = \frac{\gamma_r}{n} \sum_{j=1}^m \psi(U_{nj}^*) \phi_r(U_{nj}^*) \sum_{k=1}^{L_{nj}} X_{nrjk}^{\prime 2} + o_p(1) \\
&= \frac{\gamma_r}{n} \sum_{i=1}^n \psi(U_{ni}) \phi_r(U_{ni}) X_{nri}^2 + o_p(1) = \gamma_r E\{\psi(U) \phi_r(U)\} E(X_r^2) + o_p(1),
\end{aligned}$$

where δ_{n0jk} and δ_{nrjk} are as defined in Appendix A.3. Using Lemma 3, Lemma 4 (a.) and (31),

$$\begin{aligned}
&\sum_{j=1}^m \frac{L_{nj}}{n} \left(\frac{1}{L_{nj}} \tilde{X}_{nj}^{\prime} \tilde{X}_{nj}^{\prime} \right)_{11}^{-1} \xrightarrow{p} (\mathcal{X}^{-1})_{11}, \\
&\sum_{j=1}^m \frac{L_{nj}}{n} \tilde{X}_{nrj}^{\prime 2} \left(\frac{1}{L_{nj}} \tilde{X}_{nj}^{\prime} \tilde{X}_{nj}^{\prime} \right)_{rr}^{-1} \xrightarrow{p} \{E(X_r)\}^2 (\mathcal{X}^{-1})_{rr}.
\end{aligned}$$

Since $\hat{\gamma}_{n0} \xrightarrow{p} \gamma_0$, $\hat{\gamma}_{nr} \xrightarrow{p} \gamma_r$, $s_{\tilde{X}_r}^2 \xrightarrow{p} \text{var}(\tilde{X}_r)$ and $\tilde{X}_{nr} \xrightarrow{p} E(X_r)$, the result follows.

APPENDIX:

AUXILIARY RESULTS AND PROOFS

A.1. Additional Technical Conditions. We introduce some further technical conditions:

(C6) The functions $h_1(u) = \int x g_1(x, u) dx$ and $h_2(u) = \int x g_2(x, u) dx$ are uniformly Lipschitz, where $g_1(\cdot, \cdot)$ and $g_2(\cdot, \cdot)$ are the joint density functions of (X, U) and (Xe, U) , respectively.

(C7) The error term satisfies $E|e^\lambda| < \infty$ for $\lambda > 4$.

Conditions (C1), (C6) and (C7) are needed for the proof of Lemma 4 given in the next section.

A.2. Auxiliary results on martingale differences.

Lemma 1. *Under the technical conditions (C1)-(C6), on event A_n (11), the martingale differences Z_{n0t} satisfy the conditions*

$$(a.) \quad \sum_{t=1}^n E\{Z_{n0t}^2 I(|Z_{n0t}| > \epsilon)\} \rightarrow 0 \quad \text{for all } \epsilon > 0,$$

$$(b.) \quad \Delta_{n0}^2 = \sum_{t=1}^n Z_{n0t}^2 \xrightarrow{p} \sigma_0^2 \quad \text{for } \sigma_0^2 > 0.$$

Proof. Let $Z_{n0t} = w_{n0t}v_{n0t}$, where $w_{n0t} = 1/\sqrt{n}$, and

$$v_{n0t} = \gamma_0\psi(U_{nt}) + \psi(U_{nt})e_{nt}\{(L_{nj(t)}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)} - \gamma_0 = \alpha_{1nt} + \alpha_{2nt}e_{nt},$$

where $\alpha_{1nt} = \gamma_0\psi(U_{nt}) - \gamma_0$, $\alpha_{2nt} = \psi(U_{nt})\{(L_{nj(t)}^{-1}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)}$ and $E(v_{n0t}) = 0$. Using (C1), (C3) and (C4), it holds on event A_n that $\sup_{1 \leq t \leq n} |\alpha_{1nt}| < c_1$ and $\sup_{1 \leq t \leq n} |\alpha_{2nt}| < c_2$ for some $c_1, c_2 > 0$. Thus, it holds for $\epsilon > 0$, that

$\sum_{t=1}^n E\{Z_{n0t}^2 I(|Z_{n0t}| > \epsilon)\} = \sum_{t=1}^n \int x^2 I(|x| > \epsilon) dF_{w_{n0t}v_{n0t}}(x) = \sum_{t=1}^n \int x^2 I(|x| > \epsilon/|w_{n0t}|) w_{n0t}^2 dF_{v_{n0t}}(x) = n^{-1} \sum_{t=1}^n \int x^2 I(|x| > \sqrt{n}\epsilon) dF_{v_{n0t}}(x) \leq n^{-1} \sum_{t=1}^n \{E(v_{n0t}^4)\}^{1/2} \{P(v_{n0t}^2 > n\epsilon^2)\}^{1/2}$. Now, $E(v_{n0t}^4)$ is bounded uniformly in n and t , since e_{nt} has finite fourth moment by (C7), and $P(v_{n0t}^2 > n\epsilon^2) = P((\alpha_{1nt} + \alpha_{2nt}e_{nt})^2 > n\epsilon^2) \leq P(\alpha_{1nt}^2 + \alpha_{2nt}^2 e_{nt}^2 + 2|\alpha_{1nt}\alpha_{2nt}e_{nt}| > n\epsilon^2) \leq P(c_1^2 + c_2^2 e_{nt}^2 + 2c_1c_2|e_{nt}| > n\epsilon^2)$. Lemma 1 (a.) follows, since $P(c_1^2 + c_2^2 e_{nt}^2 + 2c_1c_2|e_{nt}| > n\epsilon^2) \rightarrow 0$ uniformly in n and t , e_{nt}^2 and $|e_{nt}|$ being i.i.d. with finite fourth moments.

The term Δ_{n0}^2 given in Lemma 1 (b.) is equal to

$$\begin{aligned} \Delta_{n0}^2 &= \gamma_0^2 \left\{ n^{-1} \sum_t \psi^2(U_{nt}) \right\} + \gamma_0^2 - 2\gamma_0^2 \left\{ n^{-1} \sum_t \psi(U_{nt}) \right\} \\ &+ 2\gamma_0 n^{-1} \sum_t \psi^2(U_{nt}) e_{nt} \{(L_{nj(t)}^{-1}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)} \\ &- 2\gamma_0 n^{-1} \sum_t \psi(U_{nt}) e_{nt} \{(L_{nj(t)}^{-1}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)} \\ &+ n^{-1} \sum_t \psi^2(U_{nt}) e_{nt}^2 \{(L_{nj(t)}^{-1}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)}^2 = T_1 + \dots + T_6. \end{aligned}$$

It follows from the law of large numbers that

$$T_1 + T_2 + T_3 \xrightarrow{p} \gamma_0^2 E\{\psi^2(U)\} + \gamma_0^2 - 2\gamma_0^2 E\{\psi(U)\} = \gamma_0^2 \text{var}\{\psi(U)\}.$$

On event A_n , $E(T_4|U, X, L_{nj}) = 0$ and

$$\text{var}(T_4|U, X, L_{nj}) = \frac{4\sigma^2\gamma_0^2}{n^2} \sum_t \psi^4(U_{nt}) \{(L_{nj(t)}^{-1}X_{nj(t)}^{IT}X'_{nj(t)})^{-1}X_{nj(t)}^{IT}\}_{1k(t)}^2 = O(n^{-1}).$$

Thus, $E(T_4) = 0$ and $\text{var}(T_4) = O(n^{-1})$, implying that $T_4 = O_p(n^{-1/2})$ on A_n . Similarly, it can be shown that $T_5 = O_p(n^{-1/2})$ on A_n .

Next consider the last term T_6 which can also be written as

$$T_6 = n^{-1} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \{(L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1} X_{nj}'^T\}_{1k}^2 \psi^2(U'_{nj k}) e_{nj k}'^2.$$

Expanding $\{(L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1} X_{nj}'^T\}_{1k}^2 \psi^2(U'_{nj k}) e_{nj k}'^2$ for each k , we get

$$\begin{aligned} T_6 &= n^{-1} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \left\{ (L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1}_{11} e'_{nj k} \psi(U'_{nj k}) + (L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1}_{12} e'_{nj k} \psi(U'_{nj k}) X'_{n1jk} + \dots \right. \\ &\quad \left. + (L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1}_{1,p+1} e'_{nj k} \psi(U'_{nj k}) X'_{npjk} \right\}^2, \end{aligned}$$

which by Lemma 4 (a.) and the law of large numbers is equal to

$$\begin{aligned} &\sigma^2 E\{\psi^2(U)\} [(\mathcal{X}^{-1})_{11}^2 + (\mathcal{X}^{-1})_{12}^2 E(X_1^2) + \dots + (\mathcal{X}^{-1})_{1,p+1}^2 E(X_p^2)] \\ &+ \{2(\mathcal{X}^{-1})_{11}(\mathcal{X}^{-1})_{12} E(X_1) + \dots + 2(\mathcal{X}^{-1})_{11}(\mathcal{X}^{-1})_{1,p+1} E(X_p)\} \\ &+ \{2(\mathcal{X}^{-1})_{12}(\mathcal{X}^{-1})_{13} E(X_1 X_2) + \dots + 2(\mathcal{X}^{-1})_{12}(\mathcal{X}^{-1})_{1,p+1} E(X_1 X_p)\} + \dots \\ &+ \{2(\mathcal{X}^{-1})_{1p}(\mathcal{X}^{-1})_{1,p+1} E(X_{p-1} X_p)\} + o_p(1) \\ &= \sigma^2 E\{\psi^2(U)\} (\mathcal{X}^{-1} \mathcal{X}^T \mathcal{X}^{-1T})_{11} + o_p(1) = \sigma^2 E\{\psi^2(U)\} (\mathcal{X}^{-1})_{11} + o_p(1), \end{aligned}$$

where \mathcal{X} is as defined in (C5) and given explicitly in (8). Thus

$$\Delta_{n0}^2 \xrightarrow{p} \gamma_0^2 \text{var}\{\psi(U)\} + \sigma^2 (\mathcal{X}^{-1})_{11} E\{\psi^2(U)\} \equiv \sigma_0^2,$$

and Lemma 1 (b.) follows.

Lemma 2. *Under the technical conditions (C1)-(C6), on event A_n (11), the martingale differences Z_{nrt} satisfy the conditions*

$$\begin{aligned} \text{(a.)} \quad &\sum_{t=1}^n E\{Z_{nrt}^2 I(|Z_{nrt}| > \epsilon)\} \rightarrow 0 \quad \text{for all } \epsilon > 0, \\ \text{(b.)} \quad &\Delta_{nr}^2 = \sum_{t=1}^n Z_{nrt}^2 \xrightarrow{p} (a, b) \Sigma_r (a, b)^T \quad \text{for } (a, b) \Sigma_r (a, b)^T > 0. \end{aligned}$$

Proof. Let $Z_{nrt} = w_{nrt} v_{nrt}$, where $w_{nrt} = 1/\sqrt{n}$, $\alpha_{3nt} = a\gamma_r \psi(U_{nt}) X_{nrt} - a\gamma_r E(X_r) + b\phi_r(U_{nt}) X_{nrt} - bE(X_r)$, $\alpha_{4nt} = a\bar{X}'_{nrj(t)} \psi(U_{nt}) \{(L_{nj(t)}^{-1} X_{nj(t)}'^T X_{nj(t)}')^{-1} X_{nj(t)}'^T\}_{rk(t)}$, $v_{nrt} = \alpha_{3nt} + \alpha_{4nt} e_{nt}$, and $E(v_{nrt}) = 0$. On event A_n , $\sup_{1 \leq t \leq n} |\alpha_{3nt}| < c_3$ and $\sup_{1 \leq t \leq n} |\alpha_{4nt}| < c_4$

for some $c_3, c_4 > 0$, and thus Lemma 2 (a.) follows in a similar fashion as Lemma 1 (a.).

The term Δ_{nr}^2 in Lemma 2 (b.) is equal to

$$\begin{aligned}
\Delta_{nr}^2 &= a^2\gamma_r^2 \left\{ n^{-1} \sum_t \psi^2(U_{nt}) X_{nrt}^2 \right\} + a^2\gamma_r^2 \{E(X_r)\}^2 + b^2 \left\{ n^{-1} \sum_t \phi_r^2(U_{nt}) X_{nrt}^2 \right\} \\
&+ b^2 \{E(X_r)\}^2 - 2a^2\gamma_r^2 E(X_r) \left\{ n^{-1} \sum_t \psi(U_{nt}) X_{nrt} \right\} + 2ab\gamma_r \{E(X_r)\}^2 \\
&+ 2ab\gamma_r \left\{ n^{-1} \sum_t \psi(U_{nt}) \phi_r(U_{nt}) X_{nrt}^2 \right\} - 2b^2 E(X_r) \left\{ n^{-1} \sum_t \phi_r(U_{nt}) X_{nrt} \right\} \\
&- 2ab\gamma_r E(X_r) \left\{ n^{-1} \sum_t \psi(U_{nt}) X_{nrt} \right\} - 2ab\gamma_r E(X_r) \left\{ n^{-1} \sum_t \phi_r(U_{nt}) X_{nrt} \right\} \\
&+ 2a^2\gamma_r n^{-1} \sum_t \psi^2(U_{nt}) e_{nt} \bar{X}'_{nrj(t)} X_{nrt} \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)} \\
&- 2a^2\gamma_r E(X_r) n^{-1} \sum_t \psi(U_{nt}) e_{nt} \bar{X}'_{nrj(t)} \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)} \\
&+ 2abn^{-1} \sum_t \psi(U_{nt}) \phi_r(U_{nt}) e_{nt} \bar{X}'_{nrj(t)} X_{nrt} \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)} \\
&- 2abE(X_r) n^{-1} \sum_t \psi(U_{nt}) e_{nt} \bar{X}'_{nrj(t)} \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)} \\
&+ a^2 n^{-1} \sum_t \psi^2(U_{nt}) e_{nt}^2 \bar{X}'_{nrj(t)} \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)}^2 = T_1 + \dots + T_{15},
\end{aligned}$$

and by the law of large numbers

$$\begin{aligned}
T_1 + \dots + T_{10} &\xrightarrow{p} a^2\gamma_r^2 [\{E(X_r)\}^2 \text{var}\{\psi(U)\} + \text{var}(X_r) E\{\psi^2(U)\}] \\
&+ 2ab\gamma_r [E\{\phi_r(U)\psi(U)\} E(X_r^2) - \{E(X_r)\}^2] + b^2 \text{var}(\tilde{X}_r).
\end{aligned}$$

On event A_n , $E(T_{11}|U, X, L_{nj}) = 0$ and

$$\text{var}(T_{11}|U, X, L_{nj}) = \frac{4a^4\sigma^2\gamma_r^2}{n^2} \sum_t \psi^4(U_{nt}) \bar{X}'_{nrj}{}^2 X_{nrt}^2 \{ (L_{nj(t)}^{-1} X_{nj(t)}'^T X'_{nj(t)})^{-1} X_{nj(t)}'^T \}_{rk(t)}^2,$$

which is $O(n^{-1})$. Thus, $E(T_{11}) = 0$ and $\text{var}(T_{11}) = O(n^{-1})$, implying that $T_{11} = O_p(n^{-1/2})$ on A_n . Similarly, it can be shown that $T_{12} = T_{13} = T_{14} = O_p(n^{-1/2})$ on A_n .

Next consider the last term T_{15} which can also be expressed as

$$T_{15} = a^2 n^{-1} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \{ (L_{nj}^{-1} X_{nj}'^T X'_{nj})^{-1} X_{nj}'^T \}_{rk}^2 \psi^2(U'_{nj(k)}) e_{nj(k)}'^2 \bar{X}'_{nrj}{}^2.$$

Again expanding $\{(L_{nj}^{-1}X_{nj}'^T X_{nj}')^{-1}X_{nj}'^T\}_{1k}^2 \psi^2(U'_{nj}) e_{nj}^{\prime 2} \bar{X}_{nrj}^{\prime 2}$ for each k , we get

$$T_{15} = a^2 n^{-1} \sum_{j=1}^m \sum_{k=1}^{L_{nj}} \left\{ (L_{nj}^{-1}X_{nj}'^T X_{nj}')_{r1}^{-1} \bar{X}'_{nrj} e'_{nj} \psi(U'_{nj}) + (L_{nj}^{-1}X_{nj}'^T X_{nj}')_{r2}^{-1} \bar{X}'_{nrj} e'_{nj} \psi(U'_{nj}) X'_{n1jk} + \dots + (L_{nj}^{-1}X_{nj}'^T X_{nj}')_{r,p+1}^{-1} \bar{X}'_{nrj} e'_{nj} \psi(U'_{nj}) X'_{npj} \right\}^2,$$

which by Lemma 4 (a.) and the law of large numbers is equal to

$$\begin{aligned} & a^2 \sigma^2 \{E(X_r)\}^2 E\{\psi^2(U)\} [(\mathcal{X}^{-1})_{r1}^2 + (\mathcal{X}^{-1})_{r2}^2 E(X_1^2) + \dots + (\mathcal{X}^{-1})_{r,p+1}^2 E(X_p^2)] \\ & + \{2(\mathcal{X}^{-1})_{r1}(\mathcal{X}^{-1})_{r2} E(X_1) + \dots + 2(\mathcal{X}^{-1})_{r1}(\mathcal{X}^{-1})_{r,p+1} E(X_p)\} \\ & + \{2(\mathcal{X}^{-1})_{r2}(\mathcal{X}^{-1})_{r3} E(X_1 X_2) + \dots + 2(\mathcal{X}^{-1})_{r2}(\mathcal{X}^{-1})_{r,p+1} E(X_1 X_p)\} + \dots \\ & + \{2(\mathcal{X}^{-1})_{rp}(\mathcal{X}^{-1})_{r,p+1} E(X_{p-1} X_p)\} + o_p(1) \\ & = a^2 \sigma^2 \{E(X_r)\}^2 E\{\psi^2(U)\} (\mathcal{X}^{-1} \mathcal{X}^T \mathcal{X}^{-1^T})_{rr} + o_p(1) \\ & = a^2 \sigma^2 \{E(X_r)\}^2 E\{\psi^2(U)\} (\mathcal{X}^{-1})_{rr} + o_p(1). \end{aligned}$$

Thus

$$\Delta_{nr}^2 \xrightarrow{p} (a, b) \Sigma_r (a, b)^T = (a, b) \begin{bmatrix} \Sigma_{r11} & \Sigma_{r12} \\ \Sigma_{r12} & \Sigma_{r22} \end{bmatrix} (a, b)^T,$$

where $\Sigma_{r11} = \gamma_r^2 [\{E(X_r)\}^2 \text{var}\{\psi(U)\} + \text{var}(X_r) E\{\psi^2(U)\}] + \sigma^2 \{E(X_r)\}^2 E\{\psi^2(U)\} (\mathcal{X}^{-1})_{rr}$, $\Sigma_{r12} = \gamma_r [E\{\phi_r(U) \psi(U)\} E(X_r^2) - \{E(X_r)\}^2]$, and $\Sigma_{r22} = \text{var}(\tilde{X}_r)$. Hence Lemma 2 (b.) follows.

A.3. Auxiliary results on approximations of inverses. Defining $\delta_{n0jk} = \psi(U'_{nj}) - \psi(U_{nj}^*)$ and $\delta_{nrjk} = \phi_r(U'_{nj}) - \phi_r(U_{nj}^*)$ for $1 \leq k \leq L_j$ and $1 \leq r \leq p$, where $U_{nj}^* = L_{nj}^{-1} \sum_{k=1}^{L_{nj}} U'_{nj}$ is the average of the U 's in B_{nj} , we obtain the following results, by Taylor expansions and boundedness considerations: for $1 \leq t, s \leq p$, $0 \leq r, r' \leq p$ and $1 \leq \ell \leq 2$, (a.) $\sup_{k,j} |U'_{nj} - U_{nj}^*| \leq (b-a)/m$; (b.) $\sup_{k,j} |\delta_{nrjk}| = O(m^{-1})$; (c.) $\sup_j |L_{nj}^{-1} \sum_k \delta_{nrjk} X_{ntjk}^\ell| = O(m^{-1})$; (d.) $\sup_j |L_{nj}^{-1} \sum_k \delta_{nrjk}^2 X_{ntjk}^\ell| = O(m^{-2})$; (e.) $\sup_j |L_{nj}^{-1} \sum_k \delta_{nrjk} X'_{ntjk} X'_{nsjk}| = O(m^{-1})$; (f.) $\sup_j |L_{nj}^{-1} \sum_k \delta_{nrjk} \delta_{nr'jk} X'_{ntjk} X'_{nsjk}| = O(m^{-2})$.

Lemma 3. Under the technical conditions (C1)-(C6), it holds on event E_n (12) that,

$$\sup_j |(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')^{-1} - (\Phi_{nj} \boxminus \Xi_{nj})| = O(m^{-1}) \mathbf{1}_{(p+1) \times (p+1)},$$

where

$$\Phi_{nj} = \begin{bmatrix} 1 & 1/\phi_1(U_{nj}^*) & \cdots & 1/\phi_p(U_{nj}^*) \\ 1/\phi_1(U_{nj}^*) & 1/\phi_1^2(U_{nj}^*) & \cdots & 1/(\phi_p(U_{nj}^*)\phi_1(U_{nj}^*)) \\ \vdots & \vdots & \ddots & \vdots \\ 1/\phi_p(U_{nj}^*) & 1/(\phi_p(U_{nj}^*)\phi_1(U_{nj}^*)) & \cdots & 1/\phi_p^2(U_{nj}^*) \end{bmatrix}, \quad (23)$$

$\Xi_{nj} = (L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1}$ and $\mathbf{1}_{(p+1) \times (p+1)}$ denotes the $(p+1) \times (p+1)$ matrix of ones.

Proof. The proof is by induction on p . Define

$$\tilde{X}_{nrj}^{(\ell)} = \frac{1}{L_{nj}} \sum_{k=1}^{L_{nj}} \tilde{X}_{nrjk}^{\ell}, \quad (\tilde{X}_{nrj}' \tilde{X}_{nsj}')^{(\ell)} = \frac{1}{L_{nj}} \sum_{k=1}^{L_{nj}} (\tilde{X}_{nrjk}' \tilde{X}_{nsjk}')^{\ell}, \quad (24)$$

and analogously for $X_{nrj}^{(\ell)}$ and $(X_{nrj}' X_{nsj}')^{(\ell)}$ where $1 \leq r, s \leq p$. First consider the claim for $p = 1$ on E_n ,

$$(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')^{-1} = \frac{1}{\tilde{X}_{n1j}^{(2)} - (\tilde{X}_{n1j}^{(1)})^2} \begin{bmatrix} \tilde{X}_{n1j}^{(2)} & -\tilde{X}_{n1j}^{(1)} \\ -\tilde{X}_{n1j}^{(1)} & 1 \end{bmatrix}.$$

By boundedness considerations and properties (c.) and (d.), it holds that $\sup_j |\tilde{X}_{n1j}^{(2)} - \phi_1^2(U_{nj}^*) X_{n1j}'^{(2)}| = O(m^{-1})$, $\sup_j |\tilde{X}_{n1j}^{(1)} - \phi_1(U_{nj}^*) X_{n1j}'^{(1)}| = O(m^{-1})$, and therefore

$$\sup_j |\{\tilde{X}_{n1j}^{(2)} - (\tilde{X}_{n1j}^{(1)})^2\} - \phi_1^2(U_{nj}^*) \{X_{n1j}'^{(2)} - (X_{n1j}'^{(1)})^2\}| = \sup_j |\tilde{d}_{nj} - \phi_1^2(U_{nj}^*) d_{nj}| = O(m^{-1}),$$

where $\tilde{d}_{nj} = \det(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')$, and $d_{nj} = \det(L_{nj}^{-1} X_{nj}'^T X_{nj}')$. Thus, $\sup_j |(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')^{-1} - (\Phi_{nj} \square \Xi_{nj})| = O(m^{-1}) \mathbf{1}_{2 \times 2}$, where $(\Phi_{nj})_{2 \times 2}$ is as given in (23), and $(\Xi_{nj})_{2 \times 2} = (L_{nj}^{-1} X_{nj}'^T X_{nj}')_{2 \times 2}^{-1}$.

Next, we show that Lemma 3 holds for $p+1$, assuming it holds for p . Let

$$(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')_{(p+2) \times (p+2)} = B_{nj} = \begin{bmatrix} B_{nj11} & B_{nj12} \\ B_{nj12}^T & B_{nj22} \end{bmatrix},$$

$$(L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')_{(p+2) \times (p+2)}^{-1} = B_{nj}^{-1} = \begin{bmatrix} B_{nj}^{11} & B_{nj}^{12} \\ B_{nj}^{12^T} & B_{nj}^{22} \end{bmatrix},$$

and similarly let

$$(L_{nj}^{-1} X_{nj}'^T X_{nj}')_{(p+2) \times (p+2)} = D_{nj} = \begin{bmatrix} D_{nj11} & D_{nj12} \\ D_{nj12}^T & D_{nj22} \end{bmatrix},$$

$$(L_{nj}^{-1} X_{nj}'^T X_{nj}')_{(p+2) \times (p+2)}^{-1} = D_{nj}^{-1} = \begin{bmatrix} D_{nj}^{11} & D_{nj}^{12} \\ D_{nj}^{12^T} & D_{nj}^{22} \end{bmatrix},$$

where $B_{nj11} = (L_{nj}^{-1} \tilde{X}_{nj}'^T \tilde{X}_{nj}')_{(p+1) \times (p+1)}$ and $D_{nj11} = (L_{nj}^{-1} X_{nj}'^T X_{nj}')_{(p+1) \times (p+1)}$. By the assumption,

$$\sup_j |B_{nj11}^{-1} - (\Phi_{nj} \square \Xi_{nj})_{(p+1) \times (p+1)}| = O(m^{-1}) \mathbf{1}_{(p+1) \times (p+1)}. \quad (25)$$

By properties (c.), (d.), (e.), (f.) and boundedness considerations, it holds that

$$\sup_j |B_{nj12} - (V_{nj} \square D_{nj12})| = O(m^{-1}) \mathbf{1}_{(p+1) \times 1}, \quad (26)$$

$$\sup_j |B_{nj22} - \phi_{n(p+1)}^2(U_{nj}^*) D_{nj22}| = O(m^{-1}), \quad (27)$$

where $B_{nj12}^T = (\tilde{X}_{n(p+1)j}'^{(1)}, (\tilde{X}_{n(p+1)j}' \tilde{X}_{n1j}')^{(1)}, \dots, (\tilde{X}_{n(p+1)j}' \tilde{X}_{npj}')^{(1)})$, $D_{nj12}^T = (X_{n(p+1)j}'^{(1)}, (X_{n(p+1)j}' X_{n1j}')^{(1)}, \dots, (X_{n(p+1)j}' X_{npj}')^{(1)})$, $B_{nj22} = \tilde{X}_{n(p+1)j}'^{(2)}$, $D_{nj22} = X_{n(p+1)j}'^{(2)}$, and $V_{nj}^T = (\phi_{p+1}(U_{nj}^*), \phi_{p+1}(U_{nj}^*) \phi_1(U_{nj}^*), \dots, \phi_{p+1}(U_{nj}^*) \phi_p(U_{nj}^*))$. Since $B_{nj}^{22} = (B_{nj22} - B_{nj12}^T B_{nj11}^{-1} B_{nj12})^{-1}$, using (25), (26), (27) and the uniform boundedness of D_{nj12} , D_{nj11}^{-1} , D_{nj22} on A_n ,

$$\sup_j |B_{nj}^{22} - \{\phi_{p+1}^2(U_{nj}^*) D_{nj}^{22}\}^{-1}| = O(m^{-1}),$$

where $\inf_j |\phi_{p+1}^2(U_{nj}^*) D_{nj}^{22}| = \inf_j |\phi_{p+1}^2(U_{nj}^*) (D_{nj22} - D_{nj12}^T D_{nj11}^{-1} D_{nj12})| > 0$, since $\phi_{p+1}(\cdot)$ is assumed to be strictly positive, and since $\sup_j |D_{nj22} - D_{nj12}^T D_{nj11}^{-1} D_{nj12}| > 0$. The latter holds on A_n , since then $\sup_j |d_j| = \sup_j |\det(D_{nj11})(D_{nj22} - D_{nj12}^T D_{nj11}^{-1} D_{nj12})| > 0$.

Now $B_{nj}^{11} = B_{nj11}^{-1} + B_{nj11}^{-1} B_{nj12} B_{nj}^{22} B_{nj12}^T B_{nj11}^{-1}$. Since D_{nj12} , D_{nj11}^{-1} are uniformly bounded on A_n ,

$$\sup_j |B_{nj}^{11} - (\Phi_{nj} \square \Gamma_{nj})| = O(m^{-1}) \mathbf{1}_{(p+1) \times (p+1)}, \quad (28)$$

where Φ_{nj} is as defined in (23), and $\Gamma_{nj} = D_{nj11}^{-1} + D_{nj11}^{-1} D_{nj12} D_{nj}^{22} D_{nj12}^T D_{nj11}^{-1} = D_{nj}^{11}$.

Since $B_{nj}^{12} = -B_{nj11}^{-1} B_{nj12} B_{nj}^{22}$, using (26), (27), (28) and boundedness considerations,

$$\sup_j |B_{nj}^{12} - (\Omega_{nj} \square \Lambda_{nj})| = O(m^{-1}) \mathbf{1}_{(p+1) \times 1},$$

where $\Omega_{nj}^T = (1/\phi_{p+1}(U_{nj}^*), 1/\{\phi_{p+1}(U_{nj}^*) \phi_1(U_{nj}^*)\}, \dots, 1/\{\phi_{p+1}(U_{nj}^*) \phi_p(U_{nj}^*)\})$, and $\Lambda_{nj} = -D_{nj11}^{-1} D_{nj12} D_{nj}^{22} = D_{nj}^{12}$. Thus, re-assembling the partitioned matrix B_{nj}^{-1} , Lemma 3 follows.

Lemma 4. *Under the technical conditions (C1)-(C7), for a sequence r_n such that $r_n = O_p\{\sqrt{(m \log n)/n}\}$, on event A_n (11)*

$$(a.) \quad \sup_j \left| (L_{nj}^{-1} X_{nj}'^T X_{nj}')^{-1} - \mathcal{X}^{-1} \right| = O_p(r_n) \mathbf{1}_{(p+1) \times (p+1)},$$

$$(b.) \quad \sup_j \left| L_{nj}^{-1} X_{nj}'^T e'_{nj} \right| = O_p(r_n) \mathbf{1}_{(p+1) \times 1},$$

where \mathcal{X} as defined in (8) is assumed to be nonsingular by (C5), and $e'_{nj} = (e'_{nj1}, \dots, e'_{njL_{nj}})^T$.

Proof. Using the sample moment notation in (24)

$$\frac{1}{L_{nj}} X'_{njT} X'_{nj} = \begin{bmatrix} 1 & X'_{n1j}^{(1)} & \dots & X'_{npj}^{(1)} \\ X'_{n1j}^{(1)} & X'_{n1j}^{(2)} & \dots & (X'_{n1j} X'_{npj})^{(1)} \\ \vdots & & \ddots & \\ X'_{npj}^{(1)} & (X'_{npj} X'_{n1j})^{(1)} & \dots & X'_{npj}^{(2)} \end{bmatrix}_{(p+1) \times (p+1)}$$

leads to

$$d_{nj} = \sum (-1)^{\text{sign}(\tau)} (L_{nj}^{-1} X'_{njT} X'_{nj})_{1\tau(1)} \dots (L_{nj}^{-1} X'_{njT} X'_{nj})_{(p+1),\tau(p+1)},$$

where the sum is taken over all permutations τ of $(1, \dots, p+1)$, and $\text{sign}(\tau)$ equals $+1$ or -1 , depending on whether τ can be written as the product of even or odd number of transpositions. The terms in the above sum have the general form

$$X'_{nr_1j}^{(1)} (X'_{n1j} X'_{nr_2j})^{(1)} \dots (X'_{npj} X'_{nr_{p+1}j})^{(1)}, \quad (29)$$

where $X'_0 = 1$ and (r_1, \dots, r_{p+1}) is a permutation of $(0, \dots, p)$. Considering the definition of the Nadaraya-Watson kernel estimator [Nadaraya (1964), Watson (1964)], we note that an arbitrary term in (29) has the form $(X'_{nsj} X'_{nr_{s+1}j})^{(1)} = \hat{m}_{nsr_{s+1}}(U_{nj}^M)$ for $0 \leq s \leq p+1$, $K(\cdot) = (1/2)\mathbf{1}_{[-1,1]}$, $h = (b-a)/m$, and $U_{nj}^M = a + (2j-1)\{(b-a)/(2m)\}$ are the midpoints of the bins B_{nj} . Uniform consistency of Nadaraya-Watson estimators with kernels of compact support has been shown in Härdle, Janssen and Serfling (1988), where

$$\sup_{a \leq u \leq b} |\hat{m}_{nsr_{s+1}}(u) - m_{sr_{s+1}}(u)| = O_p(r_n), \quad (30)$$

$m_{sr_{s+1}}(u) = E(X_s X_{r_{s+1}} | U = u) = E(X_s X_{r_{s+1}})$, and r_n is as defined in Lemma 4. Then (30) implies

$$\begin{aligned} \sup_j |\hat{m}_{nsr_{s+1}}(U_{nj}^M) - m_{sr_{s+1}}(U_{nj}^M)| &= O_p(r_n), \\ \sup_j |(X'_{nsj} X'_{nr_{s+1}j})^{(1)} - E(X_s X_{r_{s+1}})| &= O_p(r_n). \end{aligned} \quad (31)$$

Hence the uniform consistency of (29) follows, where the limit of (29) is

$$E(X_{r_1}) E(X_1 X_{r_2}) \dots E(X_p X_{r_{p+1}}), \text{ and}$$

$$\sup_j |d_{nj} - \det(\mathcal{X})| = O_p(r_n). \quad (32)$$

follows.

The cofactor of $(L_{nj}^{-1} X_{nj}'^T X_{nj})_{r\ell}$ is defined by $(-1)^{r+\ell}$ times the minor of $(L_{nj}^{-1} X_{nj}'^T X_{nj})_{r\ell}$, where the minor is the determinant after deleting the r th row and the ℓ th column of $(L_{nj}^{-1} X_{nj}'^T X_{nj})$. With a similar argument as in the case of d_{nj} , it can be shown that the minor of $(L_{nj}^{-1} X_{nj}'^T X_{nj})_{r\ell}$ is converging uniformly over j to the minor of $(\mathcal{X})_{r\ell}$ with rate r_n . Thus part (a.) of the Lemma follows. For part (b.) of the Lemma, consider

$$L_{nj}^{-1} X_{nj}'^T e'_{nj} = \left(L_{nj}^{-1} \sum_{k=1}^{L_{nj}} e'_{nj k}, L_{nj}^{-1} \sum_{k=1}^{L_{nj}} X'_{n1jk} e'_{nj k}, \dots, L_{nj}^{-1} \sum_{k=1}^{L_{nj}} X'_{n p j k} e'_{nj k} \right)^T.$$

Each term in the above sum is equal to $\hat{m}(U_{nj}^M)$, where $m(U_{nj}^M) = E(e|U) = 0$ or $m(U_{nj}^M) = E(X_r e|U) = 0$, for $r = 1, \dots, p$. Thus by the uniform consistency of $\hat{m}(U_{nj}^M)$ for $m(U_{nj}^M)$, part (b.) of the Lemma follows.

On event A_n , (32) implies that $P(\inf_j d_{nj} > \zeta) \rightarrow 1$ as $n \rightarrow \infty$, where $\zeta = \min\{\rho/2, [\inf_j(\phi_1^2(U_{nj}^*), \dots, \phi_p^2(U_{nj}^*))]^p \rho/2\}$ and ρ is as defined in (C5). We also need to show $P(\min_j L_{nj} \leq p) \rightarrow 0$ as $n \rightarrow \infty$ in order to show that $P(A) \rightarrow 1$ as $n \rightarrow \infty$. Since $P(\min_j L_{nj} > p) = 1 - P(0 \leq L_{nj} \leq p \text{ for all } j = 1, \dots, m) \geq 1 - \sum_{j=1}^m P(0 \leq L_{nj} \leq p) \geq 1 - m \sup_j P(0 \leq L_{nj} \leq p)$, it is enough to show $P(0 \leq L_{nj} \leq p) = o(m^{-1})$ uniformly in j . Now, $L_{nj} \sim \text{Bin}(n, p_{nj})$, where $c_1(b-1)/m \leq p_{nj} \leq c_2(b-a)/m$ uniformly in j , and c_1, c_2 are as given in (C1). Therefore, $mP(0 \leq L_{nj} \leq p) = m \sum_{x=0}^p p_{nj}^x (1-p_{nj})^{n-x} n! / (x!(n-x)!) \leq m \sum_{x=0}^p n^x \{c_2(b-a)/m\}^x \{1-(c_1(b-a)/m)\}^{n-x} \approx \sum_{x=0}^p m(n/m)^x \{e^{-c_1(b-a)}\}^{n/m}$, where \approx is used to denote asymptotic equivalence. The earlier made assumption of $m \log n/n \rightarrow 0$ as $n \rightarrow 0$ implies $\log m/(n/m) \rightarrow 0$ as $n \rightarrow 0$. Thus, $\log m + x \log(n/m) - n c_1(b-a)/m \rightarrow -\infty$, $m(n/m)^x \{e^{-c_1(b-a)}\}^{n/m} \rightarrow 0$ for $x = 0, \dots, p$ and $mP(0 \leq L_{nj} \leq p) \rightarrow 0$ uniformly in j as $n \rightarrow \infty$. It follows that $P(A) \rightarrow 1$ as $n \rightarrow \infty$.

Furthermore, Lemma 3 implies

$$\sup_j |\tilde{d}_{nj} - \phi_1^2(U_{nj}^*) \dots \phi_p^2(U_{nj}^*) d_{nj}| = O_p(m^{-1}).$$

This shows that $P(\inf_j \tilde{d}_{nj} > \zeta) \rightarrow 1$ as $n \rightarrow \infty$, which implies $P(\tilde{A}_n) \rightarrow 1$ as $n \rightarrow \infty$.

Thus $P(E_n) \rightarrow 1$ as $n \rightarrow \infty$.

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Table 1: Parameter estimates for the regression model $CRT = \gamma_0 + \gamma_1 CH + \gamma_2 ALB + e$, obtained by least squares regression of $\tilde{Y} = CRT$ (serum creatinine level) on $\tilde{X}_1 = CH$ (cholesterol level) and $\tilde{X}_2 = ALB$ (serum albumin level), and alternatively by covariate adjusted regression, for $n = 508$ subjects. Confidence intervals at the 95% level were obtained by the standard t -statistic for least squares regression and by the proposed asymptotic intervals (14) for CAR, respectively.

Coefficients	Least sq. Reg.			Covariate Adj. Reg.		
	Lower B.	Estimate	Upper B.	Lower B.	Estimate	Upper B.
Intercept	1.2715	4.3685	7.4656	0.3679	3.9987	7.6296
CH	-0.0106	-0.0041	0.0023	-0.0154	-0.0082	-0.0009
ALB	1.1819	1.9729	2.7639	1.3065	2.2532	3.2000

Table 2: Coverage (in percent) and mean interval length for the approximate 95% asymptotic confidence intervals formed for the parameters of the regression model (15). The values were obtained from 1000 Monte Carlo runs. The average number of points per bin was 5, 16 and 32 for sample sizes 100, 400 and 1600.

n	γ_0		γ_1		γ_2		γ_3	
	Coverage	Length	Coverage	Length	Coverage	Length	Coverage	Length
100	90.7	.56	90.4	.32	91.7	.20	96.6	.73
400	93.4	.21	94.1	.11	93.4	.06	95.5	.30
1600	94.2	.10	95.2	.05	94.7	.03	95.0	.14

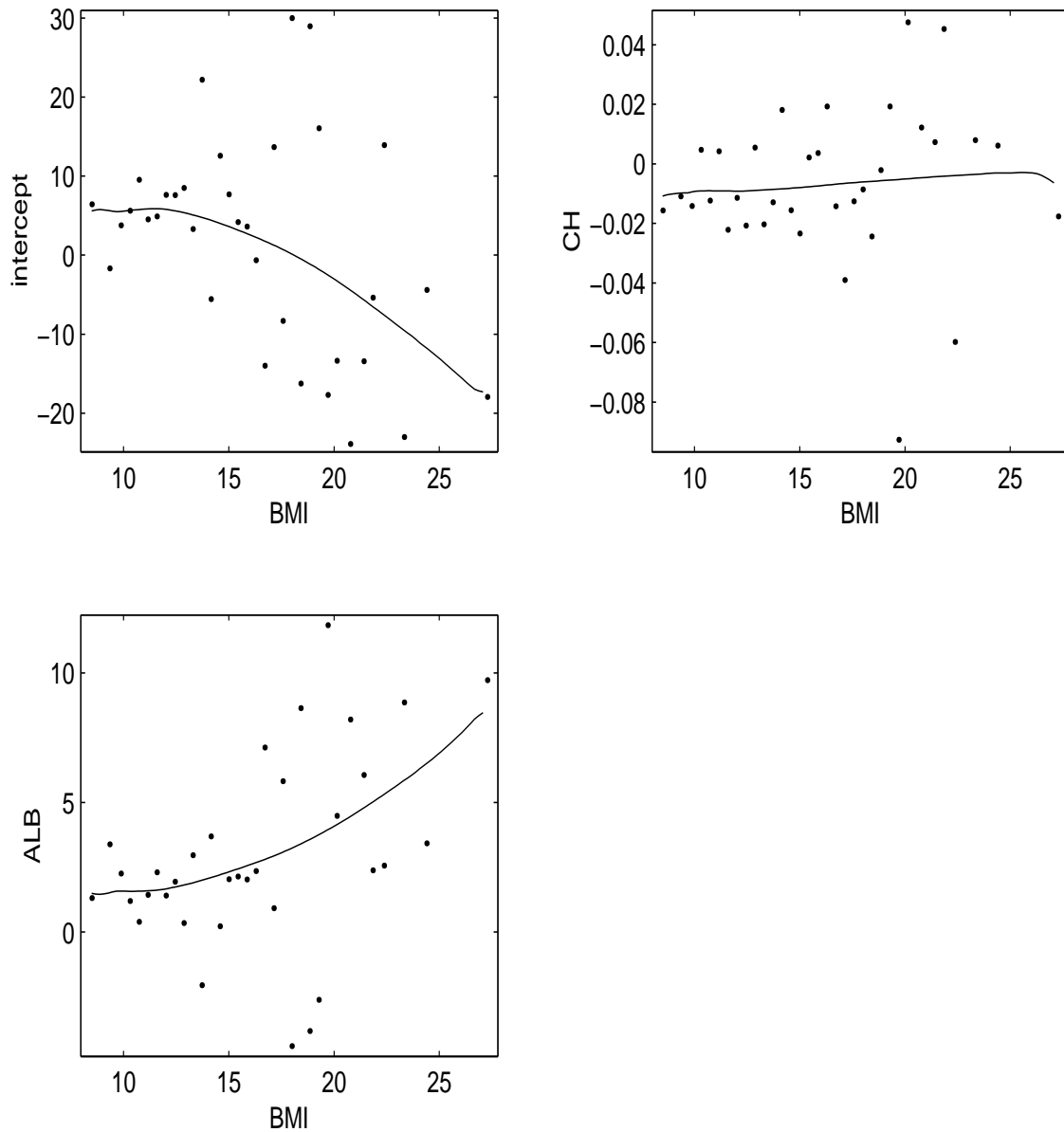


Figure 1: Scatter-plots of the raw estimates $(\hat{\beta}_{nr1}, \dots, \hat{\beta}_{nrm})$ vs. midpoints of the bins (B_{n1}, \dots, B_{nm}) for $r = 0$ (top left panel), $r = 1$ (top right panel), $r = 2$ (bottom left panel) in the CAR model $CRT = \beta_0(BMI) + \beta_1(BMI)CH + \beta_2(BMI)ALB + \epsilon(BMI)$. Local polynomial smooth curves have been fitted through the scatter plots using cross validation bandwidth choices of $h = 8, 7, 7$ respectively, for $r = 0, 1, 2$. CRT =serum creatinine level, CH =cholesterol level, ALB =serum albumin level and BMI = body mass index. Sample size is 508, and the number of bins formed is 34.