Generalized Meta-Analysis for Multivariate Regression Models Across Studies with Disparate Covariate Information

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Abstract

Meta-analysis, because of both logistical convenience and statistical efficiency, is widely popular for synthesizing information on common parameters of interest across multiple studies. We propose developing a generalized meta-analysis (GMeta) approach for combining information on multivariate regression parameters across multiple different studies which have varying level of covariate information. Using algebraic relationships between regression parameters in different dimensions, we specify a set of moment equations for estimating parameters of a “maximal” model through information available from sets of parameter estimates from a series of “reduced” models available from the different studies. The specification of the equations requires a “reference” dataset to estimate the joint distribution of the covariates. We propose to solve these equations using the generalized method of moments approach, with an optimal weighting of the equations taking into account uncertainty associated with estimates of the parameters of the reduced models. We describe extensions of the iterated reweighted least square algorithm for fitting generalized linear regression models using the proposed framework. Methods are illustrated using extensive simulation studies and a real data example involving the development of a breast cancer risk prediction model using disparate risk factor information from multiple studies.

Keywords: Generalized Method of Moments, Missing Data, Empirical Likelihood, Semiparametric Inference

1 Introduction

In a variety of domains of applications, including observational epidemiologic studies, clinical trials and modern genome-wide association studies, meta-analysis is widely used to synthesize information on underlying common parameters of interest across multiple studies [Dersimonian and Laird (1986, 2015); Ioannidis (2005); Kavvoura and Ioannidis (2008)]. Popularity of meta-analysis stems from the fact that it can be performed based only on estimates of model parameters and standard errors, avoiding various logistical, ethical and privacy concerns associated with accessing of individual level data that is required in pooled analysis. Moreover, in many common settings, it can be shown that under reasonable assumptions, meta-analyzed estimates of model parameters are asymptotically as efficient as those from pooled analysis [Olkin and Sampson (1998); Mathew and Nordstrom (1999); Lin and Zeng (2010)]. In fact, meta-analysis approaches are now being used to “divide and conquer” big data, even when individual level data are potentially available, because of the daunting computational task of model fitting with extremely large sample sizes [Jordan (2013); Jianqing et al. (2014); Chun et al. (2015)].
In this article, we study the problem of multivariate meta-analysis in the setting of parametric regression modeling of an outcome given a set of covariates. In standard settings, if estimates of multivariate parameters for an underlying common regression model and associated covariances are available across all the studies, then meta-analysis can be performed by taking inverse-variance-covariance weighted average of the vector of regression coefficients [van Houwelingen et al. (2002); Ritz et al. (2008); Jackson et al. (2011)]. In many applications, a common problem is that different studies include different, but possibly overlapping, sets of covariates. In a large consortium of epidemiologic studies, for example, typically, some key risk factors will be measured across all the studies. Inevitably, however, there will be potentially important covariates which are measured only on some, but not all the studies. Sometimes, it’s also possible that some covariates are measured at a more detailed level or with a finer instrument in some studies compared to others.

Disparate sets of covariates across studies render standard meta-analysis to be applicable for the development of models only limited to a core set of variables that are measured in the same fashion across all the studies. We propose a generalized meta-analysis (GMeta) approach that will allow development of richer models, including any covariate that is measured in at least one of the studies. We build upon a result from our recent study where we established general mathematical relationship between parameters of regression models in different dimensions. We develop a generalized method of moment estimation [Hansen (1982); Imbens (2002)] approach to make inference on parameters of the “maximal model” utilizing information on parameters and covariance matrices from a series of “reduced models”, and an additional “reference dataset” that allows estimation of the joint distribution of all the covariates under study.

In Section 2, we first introduce notations and the statistical formulation of the meta-analysis problem in the presence of disparate covariate information (Section 2.1). We then describe how information from each study can be converted into key moment equations regarding parameters of the maximal model and explain the generalized method of moment inference procedure in the fullest generality (Section 2.2). In Section 3, we describe robust computational algorithms for GMeta estimation within the class of generalized linear models using extensions of iterated reweighted least square algorithms. In Section 4, we conduct extensive simulation studies to investigate the properties of the GMeta estimates in idealized and non-idealized conditions. In Section 5, we provide an illustration of the proposed methodology to develop a model for predicting risk of breast cancer utilizing information from multiple studies that have varying level of risk-factor information. We conclude the article with discussions in Section 6.

2 Models and Methods

2.1 Model formulation

Suppose we have parameter estimates $\hat{\theta}_k$’s and associated estimates of their covariance matrices $S_k$’s from $K$ independent studies which have fitted “reduced” regression models of the form $g_k(Y | X_{A_k}; \theta_k)$, where $Y$ is a common underlying outcome of interest but the vector of covariates $X_{A_k}$ is potentially distinct across the studies. Let $X$ be the set of covariates used across all studies and we assume the true distribution of $Y$ given $X$ can be specified by a “maximal” regression model $f(Y | X; \beta)$. Our goal is to estimate and make inference about $\beta^*$, the true value of $\beta$, based on “summary-level” information, $(\hat{\theta}_k, S_k)$’s from the $K$ studies.

In the proposed setup, it is possible but not necessary, that one or more of the studies have information on all covariates to fit the maximal model by themselves. Under certain study designs, such as the multi-phase designs [Whittemore (1997); Breslow and Cain (1988); Breslow and Holubkov (1997); Scott and Wild (1997)] and the partial questionnaire design [Wacholder and Carroll...
data could be partitioned into independent sets where the maximal model can be fitted on some sets and various reduced models can be fitted on others. The maximal model \( f(Y|X; \beta) \) and the reduced models \( g_k(Y|X_{A_k}; \theta_k) \)'s may have different parametric forms, such as logistic and probit models when \( Y \) is a binary disease outcome. This setup also allows incorporation of covariates which may be measured more accurately or in a more refined fashion in some studies than others. The setup can, for example, handle the scenario where different studies may include two \( g_k \)'s which may be measured more accurately or in a more refined fashion in some studies than others. The reference sample can, for example, handle the scenario where different studies may include two different covariates which may be measured more accurately or in a more refined fashion in some studies than others. The reference dataset include both \( Z_1 \) and \( Z_2 \). One may assume that in the maximal model, \( Y \) is independent of \( Z_1 \) given \( Z_2 \) and other variables by setting the regression parameters associated with \( Z_2 \) to be zero apriori.

If all of reduced models were the same, i.e. all studies have the same covariate information, we have \( X_k = X, \theta_k = \beta \) and \( g_k = f \) for each \( k \), and the common parameter of interest \( \beta^* \) can be efficiently estimated by the fixed-effect meta-analysis estimator \( \hat{\beta}_{meta} = \sum_{k=1}^{K} (\sum_{k=1}^{K} S_k^{-1})^{-1} S_k^{-1} \hat{\theta}_k \), the variance of which, in turn, can be estimated by \( \hat{\Sigma}_{meta} = (\sum_{k=1}^{K} S_k^{-1})^{-1} \) [van Houwelingen et al. (2002); Ritz et al. (2008); Jackson et al. (2011)].

### 2.2 Generalized Meta-analysis

The key idea underlying the proposed generalized meta-analysis is that we convert information on parameters from reduced models into a set of equations that are informative about the parameters of the maximal model. In the following, we assume all studies employ a random sampling design and the same probability law for \( (Y, X) \) holds for all the underlying populations. In Section 3, we will explore possible bias due to differences in marginal distributions of \( X \) across populations.

Let \( s_k(y|x_{A_k}; \theta_k) = \frac{\partial}{\partial \theta_k} \log g_k(y|x_{A_k}; \theta_k) \) be the score function of the \( k \)th reduced model and denote \( u_k(x; \beta, \theta_k) = \int s_k(y|x_{A_k}; \theta_k)f(y|x; \beta)dy \). Assume \( \hat{\theta}_k \) is the maximum likelihood estimator from the \( k \)th study and denote \( \theta_k^* \) as the asymptotic limit of \( \hat{\theta}_k \). Irrespective of whether the reduced models are correct or not, \( E_P s_k(Y|X_{A_k}; \theta_k) = 0 \), where \( P^* \) denotes the true probability law. Assuming the maximal model is correctly specified, we can write \( P^*(Y, X_{A_k}) = \int X_{A_k} f(Y|X; \beta^*) dF^*(X) \). Hence, a general equation establishing relationship between \( \beta^* \) and \( \theta_k^* \) is in the form [Chatterjee et al. (2016)]

\[
\int u_k(x; \beta^*, \theta_k^*)dF^*(x) = 0. 
\]

As we may not have individual level data from the studies, the above equations cannot be directly evaluated. Instead, we assume that we have a reference sample of size \( n \), independent of the study samples, on which measurements on \( X \) are available. The reference sample need not to be linked with the outcome \( Y \) of interest and its sample size can be fairly modest compared to the study sample sizes (see Section 3).

With \( \theta_k \)'s from the studies and the reference sample \( \{X_i\}_{i=1}^{n} \), we can set up the estimating equations \( U_n(\beta, \hat{\theta}) = \frac{1}{n} \sum_{i=1}^{n} U(X_i; \beta, \hat{\theta}) = 0 \) with \( U(x; \beta, \theta) = (u_1^T(x; \beta, \theta_1), \ldots, u_K^T(x; \beta, \theta_K))^T, \hat{\theta} = (\hat{\theta}_1, \ldots, \hat{\theta}_K)^T \) and \( \theta = (\theta_1^T, \ldots, \theta_K^T)^T \). Suppose the dimensions of \( \theta_k \) and \( \beta \) are \( d_k \) and \( p \), respectively. Because the number of equations \( d = \sum_{k=1}^{K} d_k \) can be larger than the number of unknown parameters \( p \), the estimating equations may not be solved exactly. Following the technique of generalized method of moments (GMM), we propose the following generalized meta-analysis (GMeta) estimator of \( \beta^* \):

\[
\hat{\beta} = \arg\min_{\beta} Q_C(\beta) = \arg\min_{\beta} U_n(\beta, \hat{\theta})^T C U_n(\beta, \hat{\theta}),
\]
where \( \hat{\text{C}} \) is a positive semi-definite weighting matrix. Following the well-established theory of GMM [Hansen (1982); Engle and McFadden (1994)], we derive the asymptotic properties of the GMeta estimator. Assume the study summary statistics \( \hat{\theta}_k \)'s are independent; \( \sqrt{n_k}(\hat{\theta}_k - \theta_k) \overset{D}{\to} N(0, \Sigma_k) \) and \( \lim n_k/n = c_k > 0 \) for each \( k \); and the reference sample is independent of the study samples. Denote \( \Gamma = \mathbb{E}_{\mathbb{P}} \frac{\partial}{\partial \beta} \Lambda(U(X; \beta, \theta^*)|_{\beta=\beta^*}, \Delta = \mathbb{E}U(X; \beta^*, \theta^*)U^T(X; \beta^*, \theta^*) \) and \( \Lambda = \text{diag}(\Lambda_1, \cdots, \Lambda_K) \), where \( \Lambda_k = (1/c_k)W_k \Sigma_k W_k^T \) and \( W_k = \mathbb{E}_{\mathbb{P}} \frac{\partial}{\partial \theta_k} u_k(X; \beta^*, \theta_k) \) for each \( k \).

**Theorem 1** (Consistency and Asymptotic Normality of \( \hat{\beta} \)). Suppose the positive semi-definite weighting matrix \( \hat{\text{C}} \overset{P}{\to} \text{C} \). Then, under Assumptions (A1)-(A4) in the appendix, \( \hat{\beta} \overset{P}{\to} \beta^* \). Further, given \( \beta^* \) is an interior point and under additional Assumptions (A5)-(A9) in the appendix,

\[
\sqrt{n}(\hat{\beta} - \beta^*) \overset{D}{\to} N(0, (\Gamma^T C \Gamma)^{-1} \Gamma^T C (\Delta + \Lambda) C \Gamma (\Gamma^T C \Gamma)^{-1}).
\]

The optimal \( \text{C} \) that minimizes the above asymptotic covariance matrix is \( \text{C}_{\text{opt}} = (\Delta + \Lambda)^{-1} \) and the corresponding optimal asymptotic covariance matrix is \( (\Gamma^T (\Delta + \Lambda)^{-1} \Gamma)^{-1} \). Because \( \text{C}_{\text{opt}} \) itself depends on unknown underlying parameters, it requires iterative evaluation. In our applications, we first evaluate an initial GMeta estimator with a simple choice of \( \text{C} \) such as the identity matrix. We then obtain the iterated GMeta estimator by continuing to set \( \hat{\text{C}} = \text{C}_{\text{opt}} \) based on the latest parameter estimate till convergence. By Theorem 1, \( \hat{\beta} \) with \( \text{C}_{\text{opt}} \) approximately follows a Gaussian distribution with mean \( \beta^* \) and covariance matrix

\[
(\Gamma^T (1/\Delta + \text{diag}(1/n_1 W_1 \Sigma_1 W_1^T, \cdots, 1/n_K W_K \Sigma_K W_K^T)^{-1}) \Gamma)^{-1},
\]

which indicates that the precision of GMeta depends on the size of the reference sample \( n \) as well as on those of the studies \( n_k \)'s). However, as we will see in Section 3, the study sample sizes are the dominating factor controlling the precision of GMeta and with fixed \( n_k \)'s, the precision of GMeta quickly reaches plateau as a function of \( n \).

For the implementation of the optimal GMeta and the variance estimation of any of the GMeta estimators, one needs to have valid estimates of \( \Lambda_k \)'s, which depend on \( \Sigma_k \)'s, the asymptotic covariance matrices of the estimates of the reduced model parameters. Ideally, the studies should provide robust estimates of the covariance matrices, such as the sandwich covariance estimators, so that they are valid irrespective of whether the underlying reduced models are correctly specified or not. In practice, however, while some kind of estimates of standard errors of the individual parameters are expected to be available from a study, obtaining the desired robust estimate of the entire covariance matrix could be difficult. When no estimate of \( \Sigma_k \) is available from the \( k \)th study, one can take the advantage of the reference sample to estimate it by \( \hat{\Sigma}_k^{\text{ref}} = J^{-1} \hat{V} J^{-1} \), where \( J = \mathbb{P}_n \bar{\mathbb{E}}_Y | X \nabla_{\theta_k} s_k(\theta_k), \hat{V} = \mathbb{P}_n \hat{\mathbb{E}}_Y | X s_k(\hat{\theta}_k) s_k(\hat{\theta}_k)^T, s_k(\hat{\theta}_k) = s_k(Y | X_{A_k}; \hat{\theta}_k), \hat{\theta}_k \) is a consistent estimator of \( \theta_k^* \), \( \bar{\mathbb{E}}_Y | X \) is the expectation with respect to the distribution of \( Y | X \) with \( \beta^* \) replaced by a consistent estimator \( \hat{\beta} \), and \( \mathbb{P}_n \) is the empirical measure with respect to the reference sample. Further, given \( \mathbb{E}_Y | X \nabla_{\theta_k} s_k(\theta_k^*) = \nabla_{\theta_k} \mathbb{E}_Y | X s_k(\theta_k^*) \), it follows \( \Lambda_k = (1/c_k) \mathbb{E}(Y | X) s_k(\hat{\theta}_k) s_k(\hat{\theta}_k)^T \), which can be estimated by \( \hat{\Lambda}_k^{\text{ref}} = (1/c_k) \mathbb{P}_n \hat{\mathbb{E}}_Y | X s_k(\hat{\theta}_k) s_k(\hat{\theta}_k)^T \). For example, suppose \( Y | X \) and \( Y | X_{A_k} \) follow logistic distributions with parameters \( \beta^* \) and \( \theta_k \), respectively. Denote \( \hat{X} = (1, X^T)^T \) and \( \hat{X}_{A_k} = (1, X_{A_k}^T)^T \). Then,\n
\[
\hat{\Lambda}_k^{\text{ref}} = \frac{1}{c_k} \mathbb{P}_n \left( \frac{1}{1+e^{X_{A_k}^T \hat{\theta}_k}} \right)^2 \left( \frac{1}{1+e^{-X_{A_k}^T \hat{\theta}_k}} \right) + \left( \frac{1}{1+e^{-X_{A_k}^T \hat{\theta}_k}} \right)^2 \left( \frac{1}{1+e^{X_{A_k}^T \hat{\theta}_k}} \right) \hat{X}_{A_k} \hat{X}_{A_k}^T, \quad \text{(3)}
\]
In section 3, we will study the properties of the GMeta estimators using either covariance matrices estimated from studies or the reference sample.

It is insightful to explore the connection between GMeta and standard meta-analysis when all of the reduced models are identical to the maximal model, that is, when \( \theta_k^* = \beta^*, X_{Ak} = X \) and \( g_k = f \) for each \( k \). Under this setup, the moment vector evaluated at the true parameters becomes zero for each study, i.e. \( u_k(X; \beta^*, \theta_k^*) = u(X; \beta^*, \theta_k^*) = 0 \). This simplification implies \( \Delta = 0 \) and thus the optimal weighting matrix is given by \( C_{opt} = \Lambda^{-1} = \text{diag}(c_1 \Sigma, \ldots, c_K \Sigma) \), where \( \Sigma \) is the inverse of the Fisher’s information matrix of \( f \). Denote by \( \hat{\beta}_{opt} \) the GMeta estimator with a consistent estimator of \( C_{opt} \). Then, by arguments similar to those in the proof of Theorem 1, \( \hat{\beta}_{opt} \) can be expressed as

\[
\hat{\beta}_{opt} = \hat{\beta}_{meta} + o_p(1/\sqrt{n}), \tag{4}
\]

which implies that \( \hat{\beta}_{opt} \) and \( \hat{\beta}_{meta} \) are asymptotically equivalent in terms of limiting distributions. For more details on the derivation of (4), see Section A of Supplemental Appendix.

### 2.3 GLM and Iterated Reweighted Least Square Algorithm

GMeta computation involves minimization of a quadratic form, \( Q_C(\beta) = U_n^T(\beta, \hat{\theta})C U_n(\beta, \hat{\theta}) \), with a known weighting matrix \( C \). Next, we derive the iterated reweighted least squares algorithm for minimizing the quadratic form, assuming that the maximal and reduced models belong to the class of generalized linear models (GLM) [McCullagh and Nelder (1983)]. Specifically, the densities of the class of generalized linear models (GLM) are functions of the form \( \exp\{g(b'\psi_i) + c(y; \phi)\} \), where \( a(\cdot), b(\cdot) \) and \( c(\cdot) \) are known functions. There is a link function, \( g(\cdot) \), which is monotone and differentiable, such that \( g(b'(\psi)) = x^T \beta \) and \( g(b'(\psi)) = x^T_{Ak} \theta_k \) for the maximal and the \( k \)th reduced model, respectively.

First, we assume the dispersion parameters, \( \phi \) and \( \phi_k \)'s, are known and later we will relax this assumption. For this case, it follows, for each \( k \) and each \( i \),

\[
u_k(x_i; \beta, \theta_k) = (g^{-1}(x^T_{Xk} \beta) - g^{-1}(x^T_{Ak,k} \theta_k))(a(\phi_k)b'(\psi_{ki})g'(b'(\psi_{ki})))^{-1}x_{Ak,i}. \tag{5}\]

Let \( r_{k,i} = (g^{-1}(x^T_{Ak,k} \beta) - g^{-1}(x^T_{Ak,k} \theta_k))(a(\phi_k)b'(\psi_{ki})g'(b'(\psi_{ki})))^{-1} \) and it can be viewed as a scaled residual. Then, the moment vector is given by

\[
U_n(\beta, \theta) = \left( \frac{1}{n} \sum_{i=1}^{n} r_{1,i} x_{A1,i}^T \cdots \frac{1}{n} \sum_{i=1}^{n} r_{K,i} x_{Ak,i}^T \right)^T. \tag{6}
\]

The Newton-Raphson method for searching the minimizer of \( Q_C(\beta) \) can be written as

\[
\beta^{(t+1)} = \beta^{(t)} - \left[ X_{\text{rbind}}^T W^* X_{\text{rbind}} \right]^{-1} X_{\text{rbind}}^T W X_{A_{\text{diag}}} \left[ X_{A_{\text{diag}}}^T \right] \beta \tag{7}
\]

where \( X_{\text{rbind}} = 1 \otimes X \); \( X_{A_{\text{diag}}} = \text{diag}(X_{A1}, \ldots, X_{Ak}) \); \( W = \text{diag}(w_{11}, \ldots, w_{1n}, \ldots, w_{K1}, \ldots, w_{Kn}) \) with \( w_{ki} = \left\{ g'(g^{-1}(X_{Ak,k} \beta))g'(g^{-1}(X_{Ak,k} \theta_k))a(\phi_k)b'(\psi_{ki}) \right\}^{-1} \); \( W^* \) is the sum of \( W X_{A_{\text{diag}}} \left[ X_{A_{\text{diag}}}^T \right] \) and \( \text{diag}(r_{1,i} \otimes \lambda_{11}, \ldots, r_{1,i} \otimes \lambda_{K1}) \); and \( \lambda = \text{diag}(l_{11}, \ldots, l_{1n}, \ldots, l_{K1}) \) with \( l_{ki} = \left\{ g'(g^{-1}(X_{Ak,i} \beta))a(\phi_k)b'(\psi_{ki}) \right\} \left\{ \frac{\partial^2}{\partial y g^{-1}(y)} \right\} _y = x^T_{Ak,i} \beta \). The matrices \( W^*, W \) and the residual vector \( r \) are functions of \( \beta^{(t)} \) which gets updated at each step. Equation (7) is analogous to the \( t \)th step in the iterated reweighted least square (IRWLS) algorithm.

When \( \phi \) and \( \phi_k \)'s are unknown, we have an additional score function, denoted as \( s(\phi_k) \). Similar to equation (5), for each \( k \) and \( i \),

\[
E_{Y \mid X_i = x_i}(s(\phi_k)) = \frac{(b(\psi_{ki}) - g^{-1}(x^T_{Ak} \beta) \psi_{ki})a'(\phi_k)}{a^2(\phi_k)} + E_{Y \mid X_i = x_i} \frac{\partial c(Y_i, \phi_k)}{\partial \phi_k}.
\]
Then, the additional moment vector for $\phi$ (similar to equation (6)) is given by

$$U_n(\phi) = \left( \frac{1}{n} \sum_{i=1}^{n} u_{i1} \ldots \frac{1}{n} \sum_{i=1}^{n} u_{Ki} \right)^T,$$

where $u_{ki}(\phi) = (\rho(\hat{\phi}_k) - g^{-1}(x^T_i \beta(\hat{\phi}_k))a(\hat{\phi}_k) + q_{ki}(\phi)$ and $q_{ki}(\phi) = E_{Y_i|X_i=x_i} \frac{\partial c(Y_i, \phi)}{\partial \phi}|_{\phi_k=\hat{\phi}_k}$. As before, the Newton-Raphson steps can be written as

$$\phi^{(t+1)} = \phi^{(t)} - J_n^{-1}(\phi^{(t)})(U_n(\phi^{(t)})C \frac{\partial q_n(\phi)}{\partial \phi}|_{\phi=\phi^{(t)}}), \tag{8}$$

where $J_n(\phi) = U_n^T(\phi)C \frac{\partial^2 q_n(\phi)}{\partial \phi^2} + (\frac{\partial q_n(\phi)}{\partial \phi})^T C \frac{\partial \phi}{\partial \phi} q_n(\phi)$ and $q_n = (\frac{1}{n} \sum_{i=1}^{n} q_1(\phi) \ldots \frac{1}{n} \sum_{i=1}^{n} q_K(\phi))^T$.

To estimate $\phi^*$, the true value of $\phi$, we first choose initial estimates $\beta^{(0)}$ and $\phi^{(0)}$. Then we plug $\beta^{(0)}$ in $W$, $W^*$ and $r$ to get $\beta^{(1)}$ using equation (7). The process is repeated until a stopping rule is reached to get the GMeta estimator $\hat{\beta}$. Subsequently, $\hat{\beta}$ and $\phi^{(0)}$ are plugged in equation (8) to get $\phi^{(1)}$ and the process is repeated until a stopping rule is reached to get the final estimate of $\phi^*$. All the details are given in Section B of Supplemental Appendix.

### 3 Simulations

In this section, we study the performance of the GMeta estimators through simulation studies in both idealized and non-idealized settings. In all simulations, we assume that the relationship between a binary outcome variable $Y$ and three covariates $(X_1, X_2, X_3)$ can be described by a logistic regression model of the form

$$Y|(X_1, X_2, X_3) \sim \text{Bernoulli}(1 + \exp\{-(-\beta_0^* + \beta_1^* X_1 + \beta_2^* X_2 + \beta_3^* X_3)\})^{-1},$$

where $(X_1, X_2, X_3)$ follows a multivariate normal distribution with mean zero, unit variances and underlying correlations $\rho = (\rho_{12}, \rho_{13}, \rho_{23})$. We chose $\beta_1^* = \beta_2^* = \beta_3^* = \log 1.3$ to reflect a moderate degree of association of the outcome with each covariate after adjusting for the others. We assume existence of three separate studies, where each study fits a reduced logistic model for the outcome $Y$ on two of the covariates in the form

$$Y|(X_i, X_j) \sim \text{Bernoulli}(1 + \exp\{-(-\theta_{0,ij}^* + \theta_{i,ij}^* X_i + \theta_{j,ij}^* X_j)\})^{-1},$$

with $X_1$ and $X_2$ included in Study-I, $X_1$ and $X_3$ in Study-II and $X_1$ and $X_3$ in Study-III. We fix the sample size of the studies at $n_1 = 300$, $n_2 = 500$ and $n_3 = 1000$ and vary sample size of the reference dataset.

In the first set of simulations, we assume that the studies are conducted in the same underlying population from which the reference sample is drawn. Under this setting, there exists a common correlation vector $\rho_{db} = \rho_t = \rho_{11} = \rho_{III} = \rho_{ref}$, that describes the joint distribution of the three covariates across all the underlying populations. In a second simulation setting, we allow the correlations to vary across the populations underlying the studies as well as that underlying the reference sample to generate realistic violation of the assumption of common covariate distribution underlying GMeta. In the first setting, we chose $\rho_{db} = (0.3, 0.6, 0.1)$ so that three covariates are correlated with each other at varying levels. In the second setting, we allow two additional sets of correlation parameters, $\rho_a = (0.2, 0.4, 0.0)$ and $\rho_c = (0.4, 0.8, 0.2)$, which reflect lower- and higher- levels of correlations, respectively, across the variables, compared to the baseline value $\rho_{db}$. In all settings, we simulate data $(Y, X_1, X_2, X_3)$ for the underlying studies based on the data.
generating models as described above and fit the respective reduced models to obtain estimates of the reduced model parameters. For each set of simulated data, we obtain estimates of covariance matrices of the reduced model parameters using robust sandwich estimators based on either the study datasets themselves, or the reference dataset (see (3)). We consider three GMeta estimators: GMeta.0, which is the initial GMeta estimator with identity weighting matrix and GMeta.1 and GMeta.2, that use covariance estimates from the reference dataset and the studies, respectively.

In the first set of simulation, we assume a fixed sample size \( n = 50 \) for the reference dataset. From the results shown in Table 1, we observe that all three GMeta estimators are nearly unbiased. The standard error estimates, irrespective of whether \( \Sigma_k, k = 1, 2, 3 \) were estimated using the study data sets or the reference sample, accurately reflected the true standard errors of the GMeta parameter estimates across different simulations. As a result, the 95% confidence intervals maintained the coverage probability at the nominal level. Among the three GMeta estimators considered, clearly GMeta.0, which use the non-optimal choice of \( C = I \), is less efficient than GMeta.1 and GMeta.2, which, between themselves, had comparable efficiency.

In the same setting as above, when we vary \( n \) from 10 up to the maximum of 1000 (Figure 1), we observe that the precision of the GMeta estimates do not increase with \( n \) once it reaches a threshold around 100, which is one third of the minimum of the study sample sizes(\( n_1 = 300 \)). These thresholds were even smaller for estimation of coefficients associated with \( X_2 \), which had weak to moderate correlation with the other covariates in the model. The fact that the reference dataset can be substantially smaller than the study datasets without having much impact on the precision of the GMeta estimator is encouraging given that accessing reference dataset of large sample size may be difficult in practice.

Next, we examine the results from the simulation studies where we allowed variations in distributions in covariates across the different populations (Table 2). Here, we observe more noticeable, but still small, biases in parameter estimates. Nevertheless even in some of the worst case scenarios, the coverage probabilities of the 95% confidence intervals were 92% or higher. Intuitively, GMeta uses external information on correlations to adjust for bias in coefficient estimates of the reduced

| \( n = 50 \) | Bias | SE (ESE\(_1\), ESE\(_2\)) | RMSE | CR  | AL  |
|------------|------|-----------------------------|------|-----|-----|
| GMeta.0    | Beta | .010 (.161, .162)           | .161 | .968, .964 | .642, .636 |
|            | Beta | .005 (.111, .108)           | .110 | .958, .960 | .434, .423 |
|            | Beta | -.001 (.143, .142)          | .138 | .963, .964 | .559, .556 |
| GMeta.1    | Beta | .005 (.111, .110)           | .117 | .976, .966 | .455, .433 |
|            | Beta | -.003 (.105, .099)          | .101 | .964, .955 | .411, .386 |
|            | Beta | .001 (.102, .097)           | .099 | .973, .961 | .402, .381 |
| GMeta.2    | Beta | .007 (.111, .111)           | .115 | .971, .964 | .455, .435 |
|            | Beta | -.003 (.105, .099)          | .102 | .960, .959 | .413, .388 |
|            | Beta | .003 (.103, .098)           | .098 | .957, .957 | .403, .383 |

Table 1: Biases, standard errors (SE), estimated standard errors (ESE), square roots of mean square errors (RMSE), coverage rates (CR) and average lengths (AL) of 95% confidence intervals for GMeta.0 (the initial GMeta estimator with identity weighting matrix), GMeta.1 and GMeta.2 (the iterated GMeta estimators without and with using the study covariance estimators) in the logistic regression setting. Standard errors were estimated either using the reference sample (ESE\(_1\)) or using the covariance estimates of reduced model parameters from the studies (ESE\(_2\)). Estimated standard errors are reported by taking averages over simulated datasets. Both estimated SE’s are used to construct 95% confidence intervals and their CR’s and AL’s are reported.
Table 2: Biases, standard errors (SE), estimated standard errors (ESE), square roots of mean square errors (RMSE), coverage rates (CR), and average lengths (AL) of 95% confidence intervals of the GMeta estimation using the study covariance estimators in the setting of logistic regression with different study and reference covariate covariance matrices: $\Sigma_k$ is the covariate covariance matrix in Study $k$ for $k = 1, 2, 3$, $\Sigma_r$ is that of the reference sample, and the correlation vectors of $\Sigma_l$, $\Sigma_o$ and $\Sigma_h$ are $\rho_a = [0.2, 0.4, 0.0]$, $\rho_b = [0.3, 0.6, 0.1]$ and $\rho_c = [0.4, 0.8, 0.2]$, respectively. Estimated standard errors are obtained by the asymptotic formula (2) and used to construct 95% confidence intervals.
Table 3: Point estimators (PE) and standard errors (SE) from logistic regression with reduced and maximal models, meta-analysis and GMeta estimation with $\beta_1^* = \beta_2^* = \beta_3^* = \log(1.3) \approx .262$. NA means there is no corresponding estimator.

|                | Study I | Study II | Meta | GMeta |
|----------------|---------|----------|------|-------|
|                | Maximal | Reduced  | Reduced | Reduced | Reduced | Maximal |
| $\beta_1^*$    | .270 (.149) | .429 (.116) | .424 (.037) | .424 (.035) | .425 (.035) | .268 (.088) |
| $\beta_2^*$    | .263 (.111) | .243 (.112) | .236 (.035) | .236 (.034) | .237 (.034) | .263 (.039) |
| $\beta_3^*$    | .258 (.136) | NA       | NA     | NA     | NA     | .255 (.135) |

Finally, we conduct a third set of simulation studies to obtain more insight into results from the real data analysis (Section 4). Here, the settings are identical as before except we assume there are only two studies: study-I fits the maximal logistic regression model involving all the three covariates and study-II involves only two covariates, namely $X_1$ and $X_2$. We assume $\rho_1 = \rho_1^* = \rho_2$. In our estimation, we further considered an added complexity to account for study specific intercept terms for the maximal logistic regression model

$$Y \mid (X_1, X_2, X_3, \text{study}) \sim \text{Bernoulli}(1 + \exp\{- (\beta_{0,\text{study}}^* + \beta_1^* X_1 + \beta_2^* X_2 + \beta_3^* X_3)\}^{-1})$$

so that the prevalence of the outcome, $\text{pr}(Y = 1)$, could be different across the two studies. In this...
setting, the maximal set of parameters that are to be estimated through GMeta can be defined as \( \beta^* = (\beta_{0,\text{study-I}}, \beta_{0,\text{study-II}}, \beta_1, \beta_2, \beta_3) \). We simulated data using values of intercept parameters that are identical across the two models, but for estimation we allowed the intercept parameters to be different. For the sake of comparison, we also fitted a reduced model for study-I and conducted a standard multivariate meta-analysis of the underlying common parameters \((\theta_1 \text{ and } \theta_2)\) across the two studies. We assume the sample sizes for the two studies to be \(n_1 = 500\) and \(n_2 = 5000\), and that for the reference dataset to be \(n = 300\).

From the results reported in Table 3, we observe that in this simulation setting the reduced models produce biased estimate for \(\beta^*_1\), but not for \(\beta^*_2\). The result is intuitive given that the omitted covariate \(X_3\) is primarily correlated with \(X_1\). As a result, standard meta-analysis was nearly unbiased for \(\beta^*_2\), but not for \(\beta^*_1\). Parameter estimates from the maximal model from study-I are unbiased for all parameters, but have much larger standard error compared to meta-analysis for estimation of \(\beta^*_2\). The GMeta estimator produced unbiased estimates for all parameters and at the same time has comparable efficiency as standard meta-analysis for estimation of \(\beta^*_2\). These results highlight the desirable feature of the GMeta estimator that it can effectively combine information across studies to minimize bias due to omitted covariates and yet utilize all the information available across the partially informative studies.

### 4 Real Data Analysis

In this section, we illustrate an application of the proposed methodology to develop a model for predicting risk of breast cancer based on combination of different risk factors using data from multiple studies. The first study, the Breast Prostate Colorectal Cancer Cohort study (BPC3), includes a total of 7448 cases and 8812 controls, drawn from 8 different underlying cohorts. Details of the study, including its recent application for the development of breast cancer risk prediction model, can be found elsewhere [Mass et al. (2016)]. In the current analysis, we focus on the analysis of breast cancer risk associated with a selected set of factors, including family history (FH), age at menarche (AMEN), age at first birth (AFB) and weight (WT). The second study involves a dataset involving 1217 cases and 1616 controls from the Breast Cancer Detection and Demonstration Project (BCDDP). The study has been previously used to develop an updated version of the widely popular Breast Cancer Risk Assessment tool [Chen et al. (2006)] to incorporate mammographic density (MD), the areal proportion of breast tissue that is radiographically dense, known to be a strong risk factor for breast cancer. The dataset from the BCDDP study included mammographic density and number of previous breast biopsy (NBIOPS), in addition to all the factors considered in the BPC3 data analysis. Let \(X\) denote the common set of covariates that are measured across both the studies and \(Z\) be the factors that are available only in BCDDP. The goal is to estimate parameters associated with an underlying logistic regression model that includes all of the different factors. While the BPC3 study is large in size and represents multiple populations, it has information on more limited number of risk factors. The BCDDP study, on the other hand, has information on extended set of risk factors, but is much smaller in size. A combined analysis of these two studies can potentially lead to more generalizable and precise estimate of risk parameters.

Throughout the analysis, we used a sample of 137 cases and 163 controls from the BCDDP study as the reference sample based on which the distribution of covariates are estimated. To maintain independence of the reference and study samples, we exclude the reference sample from the primary analysis of the BCDDP study that involved estimation of the log-odds-ratio parameters. For each of the eight cohorts within the BPC3 study and for the BCDDP study, we first fit a “reduced” logistic regression model including \(X\). All models included age as an additional cofactor and included
study specific intercept parameters and age effects. Specifically, we consider underlying models in
the form
\[
(Y|X, \text{Age, study }= k) \sim \text{Bernoulli}((1 + \exp\{-(\theta_{0k} + \theta_{Ak}\text{Age} + \theta_{Xk}^T X)\})^{-1}).
\] (9)

First, to illustrate how the proposed GMeta estimator compares to standard meta-analysis
method, we consider estimating the common underlying parameters of interest \(\theta_X\) using these two
alternative methods. We fitted model (9) separately for each study and obtained estimates of the
parameters and covariance matrices. Then, for the underlying common parameter of interests \(\theta_X\),
we conducted a standard multivariate meta-analysis using the corresponding subset of parameters
estimates and covariance matrices. Alternatively, using the parameters estimates and variance-
covariance matrices from the individual studies, and using the set aside BCDDP sample as the
reference dataset to estimate the joint distribution of \(X\) and \(\text{age}\), we estimated all of the parameters
of model (9) using the GMeta procedure. From the results reported in Table 4, we observe that
in this setting, the meta-analysis and GMeta estimators produce similar estimates as well as their
standard errors across all the different risk-factors of interest. We have noted earlier that in an
idealized setting where all the models and underlying populations are identical, the two estimators
are asymptotically equivalent. It’s encouraging to observe the close correspondence between the
estimators in the data analysis, which includes a diverse set of studies that are likely to have
significant heterogeneity across the underlying populations. In particular, for a number of the
risk-factors (e.g FH), coefficient estimates were noticeably different across the BCDDP and BPC3
studies. When significant heterogeneity existed, the meta-analyzed estimates were pooled closer to
those from the BPC3 study due to its large sample size.

Next, we turn our attention to the analysis of data from the BCDDP study using a maximal
model that includes \(X\) and the additional covariates, MD and NBIOPS. Comparison of the pa-
rameter estimates associated with \(X\) across the maximal and reduced model within the BCDDP
study indicates major differences in the estimates of the coefficients associated with weight. In
the maximal model, higher weight is found to be much more strongly associated with increased
risk of breast cancer. The “unmasking” of the effect of weight in the maximal model is intuitive
given that body weight and mammographic density is known to have strong negative correlation.
Although not as dramatic, there are some differences in effects of AGEMEN and AFB between the
maximal and reduced models, also possibly because of modest correlation of these factors with MD
and NBIOPS. The effect of FH, however, is almost identical across the two models.

Finally, we used the GMeta method to combine estimates of the parameters of the maximal
model from the BCDDP study and those from the reduced models from the eight BPC3 cohorts.
We assumed an underlying “maximal” model of interest across the 9 studies in the form
\[
(Y|X, Z, \text{Age, study }= k) \sim \text{Bernoulli}((1 + \exp\{-(\theta_{0k} + \theta_{Ak}\text{Age} + \beta_X^T X + \beta_Z^T Z)\})^{-1}).
\] (10)

We observe that GMeta produces estimates of effect of FH and associated standard error very
similar to those observed based on the standard meta-analysis of the reduced models across the
nine cohorts. As noted above, the estimate is pooled heavily towards the BPC3 study due to its large
sample size. In contrast, the GMeta estimates for weight are very similar to those observed from
the maximal model only within the BCDDP study. These results are consistent with simulation
studies, where we noted earlier that GMeta behaves similar to reduced model meta-analysis when
omitted covariates do not cause notable bias. In contrast, when omitted covariates cause important
bias, the GMeta estimator is pooled towards estimates from maximal or more complete models
that may be available from a restricted set of studies. The behavior of GMeta for the two other
covariates, AGEMEN and AFB, were in between, which is also intuitive given that we had observed
their coefficients changed notably, but less dramatically, in the maximal model compared to the reduced model within the BCDDP study. The GMeta parameter estimates and standard errors for the additional variables MD and NBIOPS, were similar to those observed for the maximal model in the BCDDP, the only study which had information on these two factors. Thus, overall the data analysis illustrates that GMeta estimator behaves in a similar manner as meta-analysis for combining information across multiple possibly heterogeneous studies, but it has the added flexibility to effectively combine information from disparate models.
Table 4: Combined analysis of BCDDP and BPC3 study to develop a multivariate logistic regression model for breast cancer risk. For each cohort within BPC3 and for BCDDP, standard logistic regression model is applied for fitting reduced models including FH (family history), AMEN (age at menarche), AFB (age at first live birth) and WT (weight). Parameter estimates of the reduced models across studies are then combined using standard meta-analysis (meta) or GMeta. For the BCDDP study, a maximal logistic model is fitted including additional covariates mammographic density (MD) and number of previous biopsy (NBIOPS). These estimates are then combined with estimates of reduced model parameters from BPC3 studies to obtain GMeta estimates of the maximal model. Point estimates (PE) and standard errors (SE) are shown for each analysis. NA means there is no corresponding estimator. The variables analyzed include: FH: binary indicator of family history; AMEN1 and AMEN2: dummy variables associated with age-at-menarche categories ≥14, 12–13 and ≤11; AFB1 and AFB2: dummy variables associated with age-at-first-live-birth categories ≤20, 21–29 and ≥30; WT1 and WT2: dummy variables associated with weight categories ≤62.6, 62.6–73.1 and ≥73.1 in kilograms; NBIOPS: the number of biopsies coded as a conitunuous variable and MD: the standardized mammographic density coded as a continuous variable.
5 Discussion

In this paper, we propose generalized meta-analysis (GMeta) as an approach to develop unified regression models by combining information on parameter estimates and associated precisions from possibly disparate sub-models fitted across different studies. The proposed method can be viewed as a natural extension of the traditional fixed effect meta-analysis method that is widely used in practice. Both simulation studies and data analysis demonstrate that the method not only provides theoretically valid and efficient inference in idealized conditions, but also performs robustly in non-idealized settings.

A critical element of the proposed method is the access to a reference dataset, which is needed to estimate the joint distribution of all the covariates of interest. While the ideal choice of the reference dataset will vary by applications, publicly available survey data, which collect information on a wide variety of factors, can be useful broadly. In fact, in large scale genetic association studies, use of reference samples, such as the 1000 Genome study, are commonly used for estimation correlation parameters across genetic markers in the genome[Consortium (2012, 2015); Lee et al. (2013)]. For epidemiologic studies, good resources for reference dataset for the US population include the National Health Interview Survey(NHIS) [Bloom et al. (2010); Adams et al. (1999); Botman and Moriarity (2000)] and the National Health and Nutritional Examination Survey(NHANES) [Fang and Alderman (2000); He et al. (2001); Idler and Angel (2011); de Ferranti et al. (2006); LaKind et al. (2012)], which routinely collect data on a wide variety of health and lifestyle related factors. If multiple studies coordinate through consortium effort, which is increasingly common in biomedical applications, then studies which have most complete information, at least on some sub-samples, can provide reference sample. When information on all covariates are not available in a single reference sample, one may have to consider simulation for generating such data by combining information from multiple studies under some modeling assumptions.

As the access to large reference dataset that is ideally representative of the underlying study populations can be difficult, we found two aspects of the GMeta to be appealing. First, the sample size for the reference dataset can be small relative to the study datasets and yet GMeta can have reasonable efficiency. In fact, increasing the sample size for the reference dataset beyond certain threshold does not have an impact on the efficiency of GMeta. Second, although technically the method requires all the populations underlying the studies and the reference dataset to be the same, in practice, the method is robust to reasonable degree of heterogeneity. In particular, large bias is unlikely unless correlation among covariates are drastically different across studies.

In spite of the perceived robustness, caution is needed for interpretations and applications of models that may be developed by combining information from disparate models across multiple studies. A model developed from a single study with complete information, although may be inefficient and may lack generalizability, is more likely to be internally consistent and thus can provide valid etiologic inference even if it is not representative of the general population. On the other hand, etiologic interpretation of parameters can be difficult when the underlying model is developed using information across multiple studies that are potentially heterogeneous. For the development of predictive models, however, where the focus is not so much parameter interpretation, development of rich models by combining information across multiple studies and then validating such models in independent studies can be an appealing strategy.

In this article, we used generalized method of moments (GMM) as the underlying inferential framework. Alternatively, inference could be also performed using empirical likelihood (EL) theory [Qin and Lawless (1994); Qin (2000); Chatterjee et al. (2016)] exploiting the same set of moment equations as we propose. While in small sample, EL estimators may perform better, implementation can be substantially more complex. Recently, a simulation based method has been also described
for combining information on model parameters across disparate studies [Rahmandad et al. (2017)]. By explicitly defining the moment equations specified by reduced model parameters, we are able to frame the problem within the well established GMM inferential framework. Computationally, the proposed method may also enjoy substantial advantages in dealing with complex models, such as those in high-dimensional settings, where repeated model fitting on simulated data is extensive. Further research is merited in multiple directions to increase the practical utility of GMeta. It is possible that in some applications we may have information only on subsets of parameters underlying the fitted reduced models. It’s an open question how such partial information can be used to set up the underlying moment equations in the GMeta procedure. Ideally, to increase robustness of inference, the GMeta procedure should use study specific reference sample for setting up the moment equations. For this purpose, it may be useful to develop strategies to combine information on a common reference sample with complete covariate information and data from individual studies that have partial covariate information.

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Appendix: Proof of Theorem 1

The following is a list of assumptions for Theorem (1). Assumptions (A1)-(A4) are for consistency and the additional Assumptions (A5)-(A9) are for asymptotic normality. Checking these assumptions for logistic and linear regression models can be found in Section C of Supplementary Appendix.

(A1): \( C \) is positive semi-definite and \( C\bar{E}(X; \beta, \theta^*) = 0 \) iff \( \beta = \beta^* \).

(A2): \( \beta^* \in D_\beta \), which is compact.

(A3): \( u_k(X; \beta, \theta_k) \) is continuous for each \( (\beta, \theta_k) \in D_\beta \times N(\theta_k^*) \) with probability one, where \( N(\theta_k^*) \) is a neighborhood of \( \theta_k^* \) for each \( k \).

(A4): \( \bar{E}\sup_{(\beta, \theta_k) \in D_\beta \times N(\theta_k^*)} ||u_k(X; \beta, \theta_k)|| < \infty \) for each \( k \).

(A5): \( \frac{\partial}{\partial \theta_k} u_k(X; \beta, \theta_k) \) is continuous at each \( (\beta, \theta_k) \in N(\beta^*) \times N(\theta_k^*) \) with probability 1, where \( N(\beta^*) \) is a neighborhood of \( \beta^* \).

(A6): \( \bar{E}\sup_{(\beta, \theta_k) \in N(\beta^*) \times N(\theta_k^*)} ||\frac{\partial}{\partial \beta} u_k(X; \beta, \theta_k)|| < \infty \).

(A7): \( \frac{\partial}{\partial \theta_k} u_k(X; \beta^*, \theta_k) \) is continuous at each \( \theta_k \in N(\theta_k^*) \) with probability one.

(A8): \( \bar{E}\sup_{\theta_k \in N(\theta_k^*)} ||\frac{\partial}{\partial \theta_k} u_k(X, \beta^*, \theta_k)|| < \infty \).

(A9): \( \Delta(\beta^*, \theta^*) \) exists and is finite and \( \Gamma(\beta^*, \theta^*) \) is of full rank.

Proof of Theorem 1. This is a sketch of the proof. The full proof is in Section C of Supplementary Appendix. First, we show the consistency of \( \hat{\beta} \). Denote \( \hat{\theta} = (\hat{\theta}_1^T, \hat{\theta}_2^T, \cdots, \hat{\theta}_K^T)^T \), \( \theta^* = (\theta_1^T, \theta_2^T, \cdots, \theta_K^T)^T \), \( U_0(\beta, \theta) = \bar{E}(X; \beta, \theta) \) and \( Q(\beta) = U_0(\beta, \theta^*)^T C U_0(\beta, \theta^*) \). By (A1), \( Q(\beta) \) is uniquely minimized at \( \beta^* \). By (A2), (A3) and (A4), \( U_0(\beta, \theta^*) \) is continuous for \( \beta \in D_\beta \); both \( U_n(\beta, \hat{\theta}) - U_0(\beta, \hat{\theta}) \) and \( U_n(\beta, \hat{\theta}) - U_0(\beta, \theta^*) \) converges uniformly in probability to 0 for
\( \beta \in \mathbf{D}_\beta \). Then, \( U_n(\beta, \hat{\theta}) \) converges uniformly in probability to \( U_0(\beta, \theta^*) \) for \( \beta \in \mathbf{D}_\beta \). By the triangle and Cauchy-Schwartz inequalities, 
\[
|Q_n(\beta) - Q(\beta)| \leq ||U_n(\beta, \hat{\theta}) - U_0(\beta, \theta^*)||^2 ||\hat{C}|| + 2||U_0(\beta, \theta^*)|| ||U_n(\beta, \hat{\theta}) - U_0(\beta, \theta^*)|| ||\hat{C}|| + ||U_0(\beta, \theta^*)||^2 ||\hat{C} - C||. 
\]
Thus, \( Q_n(\beta) - Q(\beta) \) converges uniformly in probability to 0 for \( \beta \in \mathbf{D}_\beta \). By Theorem 2.1 of Newey and McFadden (1994), \( \hat{\beta} \) is a consistent estimator of \( \beta^* \).

Next, we derive the asymptotic distribution of the GMeta estimator \( \hat{\beta} \). Note that \( \hat{\beta} \) is a solution to \( G_n(\beta, \hat{\theta}) = 0 \) with \( G_n(\beta, \hat{\theta}) = \frac{\partial}{\partial \beta} U_n(\beta, \hat{\theta}) \), the Jacobian of \( U_n(\beta, \hat{\theta}) \). On the other hand, by the Mean Value Theorem, \( U_n(\beta, \hat{\theta}) = U_n(\beta^*, \hat{\theta}) + G_n(\beta, \hat{\theta})(\hat{\beta} - \beta^*) \), where \( \beta \) is a matrix each column of which corresponds to each element of \( U_n(\beta, \hat{\theta}) \). After left multiplying \( G_n(\beta, \hat{\theta})^T \hat{C} \) to the above identity, it follows \( \sqrt{n}(\hat{\beta} - \beta^*) = -M_n \sqrt{n} U_n(\beta^*, \hat{\theta}) \), where \( M_n = [G_n(\beta, \theta)^T \hat{C} G_n(\beta, \hat{\theta})]^{-1} G_n(\beta, \hat{\theta})^T \hat{C} \).

Consider \( M_n \). Since \( \hat{\beta} \) is a consistent estimator of \( \beta^* \), each column of \( \hat{\beta} \) is a consistent estimator of \( \beta^* \). On the other hand, \( \hat{\theta} \) is a consistent estimator of \( \theta^* \). By (A5) and (A6), both \( G_n(\beta, \hat{\theta}) \) and \( G_n(\beta, \hat{\theta}) \) converges in probability to \( \Gamma \). Thus, by noting \( \hat{C} \overset{P}{\rightarrow} C \), \( M_n \) converges in probability to \( (\Gamma^T C \Gamma)^{-1} \Gamma^T C \).

Consider \( \sqrt{n} U_n(\beta^*, \hat{\theta}) \). By the Mean Value Theorem, \( U_n(\beta^*, \hat{\theta}) = U_n(\beta^*, \theta^*) + V_n(\beta^*, \hat{\theta})(\hat{\theta} - \theta^*) \), where \( V_n \) is the Jacobian of \( U_n(\beta^*, \hat{\theta}) \) as a function of \( \theta \) and \( \hat{\theta} \) is a matrix each column of which corresponds to each element of \( U_n(\beta^*, \hat{\theta}) \). Thus, \( \sqrt{n} U_n(\beta^*, \hat{\theta}) = \sqrt{n} U_n(\beta^*, \theta^*) + V_n(\beta^*, \hat{\theta}) \sqrt{n}(\theta - \theta^*) \). By (A9) and Central Limit Theorem, \( \sqrt{n} U_n(\beta^*, \theta^*) \overset{D}{\rightarrow} N(0, \Delta) \). Since \( \theta \) is a consistent estimator of \( \theta^* \), each column of \( \hat{\theta} \) converges in probability to \( \theta^* \). By (A7) and (A8), \( V_n(\beta^*, \hat{\theta}) \overset{P}{\rightarrow} \operatorname{diag}(W_1, W_2, \cdots, W_K) \), where, for \( k = 1, 2, \cdots, K \), \( W_k = E \frac{\partial}{\partial \theta_k} u_k(X; \beta^*, \theta_k) |_{\theta_k = \theta_k^*} \). Note that the \( K \) study data sets are independent. So are \( \theta_k \)'s. Note that \( n_k = c_k n \), where \( c_k \) is a positive constant for \( k = 1, 2, \cdots, K \). Then \( \sqrt{n}(\theta - \theta^*) \) converges in distribution to \( N(0, \operatorname{diag}((1/c_1) \Sigma_1, (1/c_2) \Sigma_2, \cdots, (1/c_K) \Sigma_K)) \). Since the \( K \) data sets and the reference data are independent, the above results imply that \( \sqrt{n} U_n(\beta^*, \hat{\theta}) \overset{D}{\rightarrow} N(0, \Lambda + \Delta) \), where \( \Lambda \) is a block diagonal matrix whose \( k \)th block is \( \frac{1}{c_k} W_k \Sigma_k W_k^T \) for \( k = 1(1)K \). Therefore, by Slutsky’s theorem, we have \( \sqrt{n}(\hat{\beta} - \beta^*) \overset{D}{\rightarrow} N(0, (\Gamma^T C \Gamma)^{-1} \Gamma^T C (\Lambda + \Delta) C (\Gamma^T C \Gamma)^{-1}) \).

**More on the global identification assumption (A1):** Sometimes it’s difficult to practically check the global identification condition. This motivates us to identify the parameter locally which is equivalent to saying that the matrix of second derivatives at the true parameter, i.e., \( \frac{\partial^2}{\partial \beta \beta^T} Q(\beta)|_{\beta = \beta^*} = [E \frac{\partial}{\partial \beta} U(X; \beta)]^T C [E \frac{\partial}{\partial \beta} U(X; \beta)] |_{\beta = \beta^*} \) is a positive definite matrix [Rothenberg (1971), Engle and McFadden (1994)] assuming \( C \) to be a positive definite matrix. The corresponding sample version is that the matrix \( X_{rbind}^T W X_{A_{diag}} C X_{A_{diag}}^T W X_{rbind} \) (the first term of the hessian matrix in the Newton’s method) is positive definite (or equivalently non-singular, as it is already a positive semi-definite matrix). Given \( C \) is positive definite, the local identifiability condition for the sample version then becomes that \( X_{A_{diag}}^T W X_{rbind} \) is of full column rank. A sufficient condition for this is that \( X_{A_{diag}} \) contains information on all the covariates of the full model. In other words, each of the covariates in the maximal model is in at least one of the reduced models.

**Supplementary Appendix**

Additional materials can be found in the file of Supplementary Appendix.
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Supplementary Appendix for the Paper:

“Generalized Meta-Analysis for Multivariate Regression Models Across Studies with Disparate Covariate Information”

by Runlong Tang, Prosenjit Kundu and Nilanjan Chatterjee

A Asymptotic Equivalence of GMeta Estimator and Simple Meta-Analysis Estimator When All the Reduced Models Are the Same to the Maximal Model

In this subsection, we derive the equation (4) in the paper. When all the reduced models are the maximal model, it follows \( \theta_k^* = \beta^* \), \( X_{Ak} = X \) and \( g_k = f \) for \( k = 1, 2, \ldots, K \). Then, for each \( k \), \( u_k(X; \beta^*, \theta_k^*) = u_k(X; \beta^*, \beta^*) = \int s_k(y|X_{Ak}; \beta^*)f(y|X; \beta^*)dy = 0 \). By the definition of \( \Delta \), we have \( \Delta = 0 \). On the other hand, given \( E_Y X \nabla \theta_n s_k(\theta_k^*) = \nabla \theta_n E_Y s_k(\theta_k^*) \) with \( s_k(\theta_k^*) = s_k(Y|X_{Ak}; \theta_k^*) \), it follows \( \Delta_k = (1/c_k)I(\theta_k^*) \), where \( I(\theta_k^*) \) is the Fisher’s information matrix. Then, the optimal \( C \) is given by

\[
C_{opt} = \Lambda^{-1} = \text{diag}(c_1 \Sigma, \ldots, c_K \Sigma),
\]

where \( \Sigma = I(\theta_k^*)^{-1} \). Denote as \( \hat{C}_{opt} \) a consistent estimator of \( C_{opt} \). Then, the GMeta estimator with \( \hat{C}_{opt} \) is given by

\[
\hat{\beta}_{opt} = \arg\min_{\beta} U_n^T(\beta; \hat{\theta}) \hat{C}_{opt} U_n(\beta; \hat{\theta}).
\]

Under regularity conditions similar to those in Theorem 1, \( \hat{\beta}_{opt} \xrightarrow{P} \beta^* \). By mean-value theorem,

\[
U_n(\hat{\beta}_{opt}; \hat{\theta}) = U_n(\beta^*; \hat{\theta}) + G_n(\hat{\beta}; \hat{\theta})(\hat{\beta}_{opt} - \beta^*), \tag{11}
\]

where \( \hat{\beta} \) is the mean value and \( G_n(\hat{\beta}; \hat{\theta}) = \frac{\partial}{\partial \beta} U_n(\beta; \hat{\theta})|_{\beta = \beta^*} \). By the first order condition, \( \hat{\beta}_{opt} \) satisfies \( G_n^T(\hat{\beta}_{opt}; \hat{\theta}) \hat{C}_{opt} U_n(\hat{\beta}_{opt}; \hat{\theta}) = 0 \). Left-multiplying (11) by \( G_n^T(\hat{\beta}_{opt}; \hat{\theta}) \hat{C}_{opt} \), it follows

\[
\hat{\beta}_{opt} - \beta^* = -[G_n^T(\hat{\beta}_{opt}; \hat{\theta}) \hat{C}_{opt} G_n(\beta; \hat{\theta})]^{-1}[G_n^T(\hat{\beta}_{opt}; \hat{\theta}) \hat{C}_{opt} U_n(\beta^*; \hat{\theta})]. \tag{12}
\]

Note that

\[
G_n(\hat{\beta}_{opt}; \hat{\theta}) = \frac{\partial}{\partial \beta} U_n(\beta; \hat{\theta})|_{\beta = \hat{\beta}_{opt}} = \begin{pmatrix}
\frac{\partial}{\partial \beta^1} u_1(\beta; \hat{\theta})|_{\beta = \hat{\beta}_{opt}} \\
\vdots \\
\frac{\partial}{\partial \beta^K} u_K(\beta; \hat{\theta})|_{\beta = \hat{\beta}_{opt}}
\end{pmatrix}.
\]

Under regularity conditions similar to those in Theorem 1, \( \frac{\partial}{\partial \beta^k} u_k(\beta; \hat{\theta})|_{\beta = \hat{\beta}_{opt}} = \Sigma^{-1} + o_p(1) \) for each \( k \). Then,

\[
G_n(\hat{\beta}_{opt}; \hat{\theta}) = \begin{pmatrix}
\Sigma_1^{-1} \\
\vdots \\
\Sigma_K^{-1}
\end{pmatrix} + o_p(1). \tag{13}
\]

Similarly,

\[
G_n(\hat{\beta}; \hat{\theta}) = \begin{pmatrix}
\Sigma_1^{-1} \\
\vdots \\
\Sigma_K^{-1}
\end{pmatrix} + o_p(1). \tag{14}
\]
On the other hand, under regularity conditions similar to those in Theorem 1, \( u_k(\beta^*; \hat{\theta}_k) = -\Sigma^{-1}(\hat{\theta}_k - \beta)^* + o_p(1/\sqrt{n}) \). Then,

\[
U_n(\beta^*; \hat{\theta}) = -\begin{pmatrix}
\Sigma^{-1}(\hat{\theta}_1 - \beta^*) \\
\vdots \\
\Sigma^{-1}(\hat{\theta}_K - \beta^*)
\end{pmatrix} + o_p(1/\sqrt{n}).
\]

Hence, by (12), (13), (14), (15) and Slutsky’s Theorem,

\[
\hat{\beta}_{opt} - \beta^* = (\sum_{k=1}^K c_k)^{-1} \left( \sum_{k=1}^K c_k (\hat{\theta}_k - \beta^*) \right) + o_p(1/\sqrt{n}).
\]

On the other hand,

\[
\hat{\beta}_{meta} - \beta^* = \left( \sum_{k=1}^K \left( \frac{\hat{\Sigma}_k}{n_k} \right)^{-1} \right)^{-1} \left( \sum_{k=1}^K \left( \frac{\hat{\Sigma}_k}{n_k} \right)^{-1} \hat{\theta}_k \right) - \beta^*
\]

\[
= \left( \sum_{k=1}^K c_k \right)^{-1} \left( \sum_{k=1}^K c_k (\hat{\theta}_k - \beta^*) \right) + o_p(1/\sqrt{n}).
\]

Therefore, by (16) and (17), \( \hat{\beta}_{opt} = \hat{\beta}_{meta} + o_p(1/\sqrt{n}) \).

\section*{B IRWLS Algorithm}

\subsection*{B.1 Derivation of the IRWLS algorithm}

In this section we provide a rigorous derivation of the Newton’s method. As in Section 2.3, we assume the link function, \( g \), to be same for both the maximal and the reduced models. However, the method is flexible to have different link functions. If the estimates of the dispersion parameters, \( \phi_k \)'s are not provided directly or indirectly (obtained from estimates of variance-covariance matrices which are given), we assume the outcomes, \( Y \)'s, are standardized (var(\( Y \)) = 1) to obtain estimates of the function of dispersion parameters, \( a(\phi) \)'s, through the following relation obtained from conditional variance formula

\[
a(\hat{\phi}_k) = \left[ 1 - \left\{ \frac{1}{n} \sum_{i=1}^n \left( g^{-1}(x_{Ak,i}^T \hat{\theta}_k) - g^{-1}(x^T \theta) \right)^2 \right\} \right]^{-1} E_{P_n}(b''(\hat{\psi}_k)),
\]

where \( g^{-1}(x^T \theta) = \frac{1}{n} \sum_{i=1}^n g^{-1}(x_{Ak,i}^T \hat{\theta}_k) \) and \( P_n \) is the empirical distribution. For normal family where the canonical link is an identity function, we have \( b''(\psi) = 1 \) which implies \( E_{P_n}(b''(\hat{\psi}_k)) = 1 \). For binomial family where the canonical link is logit, we don’t have any dispersion parameter. For other families, \( b''(\psi) \) might depend on \( \theta \) and \( x \)'s in which \( E_{P_n}(b''(\hat{\psi}_k)) \) is computed from reference data, \( x_{Ak,i} \)'s and reduced parameter estimates, \( \theta_k \)'s.

\textbf{Case I : } \( \phi \) is known.
B.1.1 Steps towards setting the moment function

Assume $Y|Z$ follows a distribution from exponential family:

$$f_Y(y; \psi, \phi|Z) = \exp\left\{ \frac{y\psi - b(\psi)}{a(\phi)} + c(y; \phi) \right\},$$

and the link function is strictly monotone and differentiable. Then, $b(\psi) = E(Y|Z) = g^{-1}(Z^T\beta)$ and $b''(\psi) = \frac{\text{Var}(Y|Z)}{a(\phi)}$.

The set of covariates in the maximal model, denoted by the vector $X$, is constructed by taking the union of all the covariates in the reduced models. Mathematically we have $X = \bigcup_{k=1}^{K} X_{Ak}$ where $X_{Ak}$ denotes the set of covariates in the $k$th reduced model. The maximal model is given by

$$g(E(Y|X)) = X^T\beta,$$

where $Y$ is a scalar, $X$ is a $p \times 1$ vector and $\beta$ is a $p \times 1$ vector.

The reduced model of the $k$th study is given by

$$g_k(E(Y|X_{Ak})) = X_{Ak}^T\theta_k,$$

where $Y$ is a scalar, $X_{Ak}$ is a $d_k \times 1$ vector and $\theta_k$ is a $d_k \times 1$ vector.

Then, the Log-likelihood of $g_k$ is given by

$$l(\theta_k|Y, X_{Ak}) = \frac{Y\psi_k - b(\psi_k)}{a(\phi)} + c(Y; \phi).$$

By chain rule, the score function for $i$th individual is given by

$$s(\theta_k|Y_i, X_{Ak,i}) = (Y_i - g^{-1}(X_{Ak,i}^T\theta_k))(a(\phi_k)b''(\psi_{ki})g'(b'(\psi_{ki})))^{-1}X_{Ak,i}.$$

Denote $s(\theta_k|Y_i, X_{Ak,i})$ by $s(\theta_k)$. Then,

$$E_{Y_i|X_i}(s(\theta_k)) = (g^{-1}(X_i^T\beta) - g^{-1}(X_{Ak,i}^T\theta_k))(a(\phi_k)b''(\psi_{ki})g'(b'(\psi_{ki})))^{-1}X_{Ak,i}.$$

Thus, the empirical vector of moment functions for $\beta$ is given by

$$U_n(\beta) = \left( \begin{array}{c} \frac{1}{n} \sum_{i=1}^{n}(g^{-1}(X_i^T\beta) - g^{-1}(X_{Ak,i}^T\hat{\theta}_{Ak,i}))(a(\hat{\phi}_1)b''(\hat{\psi}_{1i})g'(\hat{b}'(\hat{\psi}_{1i})))^{-1}X_{A_{1,i}} \\
\frac{1}{n} \sum_{i=1}^{n}(g^{-1}(X_i^T\beta) - g^{-1}(X_{Ak,i}^T\hat{\theta}_{Ak,i}))(a(\hat{\phi}_2)b''(\hat{\psi}_{2i})g'(\hat{b}'(\hat{\psi}_{2i})))^{-1}X_{A_{2,i}} \\
\vdots \\
\frac{1}{n} \sum_{i=1}^{n}(g^{-1}(X_i^T\beta) - g^{-1}(X_{Ak,i}^T\hat{\theta}_{Ak,i}))(a(\hat{\phi}_K)b''(\hat{\psi}_{Ki})g'(\hat{b}'(\hat{\psi}_{Ki})))^{-1}X_{A_{K,i}} \end{array} \right),$$

where $U_n(\beta)$ is a $\sum_{k=1}^{K} d_k \times 1$ vector. We also assume $d = \sum_{k=1}^{K} d_k > p$.

B.2 Newton-Raphson (NR) Method

Let $Q_n(\beta) = U_n^T(\beta)CU_n(\beta)$ where $C$ is a $d \times d$ positive definite matrix. The goal is to minimize $Q_n(\beta)$ with respect to $\beta$. Its equivalent to solving the equation

$$D_n(\beta) = 0,$$

where $D_n(\beta) = \frac{\partial Q_n(\beta)}{\partial \beta} = U_n^T(\beta)C\frac{\partial U_n(\beta)}{\partial \beta}$ is a $1 \times p$ vector. Also $\frac{\partial U_n(\beta)}{\partial \beta}$ is a $d \times p$ matrix. The $t$th iteration step for the NR method is given by

$$\beta^{(t+1)} = \beta^{(t)} - \{J_n(\beta^{(t)})\}^{-1}\{D_n(\beta^{(t)})\}^T,$$

where $J_n(\beta^{(t)}) = \frac{\partial D_n(\beta)}{\partial \beta} |_{\beta=\beta^{(t)}}$ is a $p \times p$ matrix.
B.2.1 Explicit Expression of $D_n(\beta)$ in Matrix Form

Let $w_{ki} = \left\{ g'\left(g^{-1}(X_i^T \beta)\right)g'\left(g^{-1}(X_{Ak_i}^T \hat{\theta}_{Ak_i})a(\hat{\phi}_k)b'(\hat{\psi}_ki))\right) \right\}^{-1}$. Then,

$$\frac{\partial U_n(\beta)}{\partial \beta} = \left( \begin{array}{cccc} \sum_{i=1}^{n} w_{i1} X_i X_{A_1,i} & \cdots & \sum_{i=1}^{n} w_{id} X_i X_{A_d,i} \\ \vdots & \ddots & \vdots \\ \sum_{i=1}^{n} w_{Ki} X_i X_{A_k,i} & \cdots & \sum_{i=1}^{n} w_{Kd} X_i X_{A_k,i} \end{array} \right)_{\sum_{i=1}^{K} d_i \times d}$$

$$= \left[ X_{A_1}^T \ 0 \ \cdots \ 0 \\
0 \ \ X_{A_2}^T \ \cdots \ 0 \\
\vdots \ \ \ \ \vdots \\
0 \ 0 \ \cdots \ X_{A_K}^T \right] \left[ W_1 \ 0 \ \cdots \ 0 \\
0 \ W_2 \ \cdots \ 0 \\
\vdots \\
0 \ \cdots \ W_K \right] \left[ X \right]$$

$$= X_{A_{bind}(d \times nK)}^T W_{(nK \times nK)} X_{rbind(nK \times p)} \left( \frac{1}{K} \sum_{i=1}^{K} d_i \times 1 \right)$$

where $X_{A_{bind}}$ is a $nK \times d$ matrix constructed from combining the data matrices (each in each blocks respectively) from each of the studies, $W = \text{diag}(W_1, \ldots, W_K)$ and $W_k = \text{diag}(w_{k1}, \ldots, w_{kn})$ for $k = 1, \ldots, K$ and $X_{rbind} = 1 \otimes X$ is a $nK \times p$ matrix obtained by stacking the reference data matrix for $K$ times.

Similarly, the matrix form of $U_n(\beta)$ is given by

$$U_n(\beta) = (X_{A_{bind}}^T r)_{(\sum_{i=1}^{K} d_i \times 1)}$$

where $r = (r_1 \ldots r_K)^T$ denotes the vector of residuals, $r_k = (r_{k1} \ \cdots \ r_{kn})^T$ and $r_{ki} = (g^{-1}(X_i^T \beta) - g^{-1}(X_{Ak_i}^T \hat{\theta}_{Ak_i})) \left( b'(\hat{\psi}_ki)g'(b'(\hat{\psi}_ki)) \right)^{-1}$, which can be interpreted as the residual, for $i = 1, \ldots, n; k = 1, \ldots, K$. Plugging the above expressions in $D_n(\beta)$, we get

$$(D_n(\beta))^T = X_{rbind}^T W X_{A_{bind}} C X_{A_{bind}}^T r. \quad (19)$$

B.2.2 Explicit Expression of $J_n(\beta)$ in Matrix Form

Denote $\frac{\partial}{\partial \beta} U_n(\beta)$ by $U_n'(\beta)$, which is a $d \times p$ matrix. Let $U_n'(\beta)$ be partitioned by columns as $U_n'(\beta) = [U_{n,1}'(\beta) \ \cdots \ U_{n,d}'(\beta)]$, where $U_{n,j}'(\beta)$ denotes a $d \times 1$ vector for $j = 1, \ldots, p$.

Note that

$$J_n(\beta) = \frac{\partial}{\partial \beta} D_n(\beta) = \frac{\partial}{\partial \beta} U_n'(\beta) C U_n'(\beta)$$

$$= \begin{pmatrix} \frac{\partial}{\partial \beta} U_n'(\beta) C U_{n,1}'(\beta) \\
\vdots \\
\frac{\partial}{\partial \beta} U_n'(\beta) C U_{n,d}'(\beta) \end{pmatrix} = \begin{pmatrix} U_{n,1}'(\beta) C U_{n,1}'(\beta) + U_{n,1}'(\beta) C \frac{\partial}{\partial \beta} U_{n,1}'(\beta) \\
\vdots \\
U_{n,d}'(\beta) C U_{n,d}'(\beta) + U_{n,d}'(\beta) C \frac{\partial}{\partial \beta} U_{n,d}'(\beta) \end{pmatrix}. \quad (20)$$

Then, $U_{n,j}'(\beta) = X_{A_{bind}}^T W X_{rbind,j}$ for each $j$. Therefore, the first summation part in the $j$th row of $J_n(\beta)$ is equal to $X_{rbind,j}^T W X_{A_{bind}} C X_{A_{bind}}^T W X_{rbind}$ and the second summation part is equal to $r^T X_{A_{bind}} C \frac{\partial}{\partial \beta} U_{n,j}'(\beta)$. Then, for each $j$,

$$\frac{\partial}{\partial \beta} U_{n,j}'(\beta) = X_{A_{bind}}^T L_{(nK \times nK)} X_{A_{bind}(nK \times nK)}^T X_{rbind},$$
where \( \mathbf{L} = \begin{bmatrix} \mathbf{L}_1 & 0 & \cdots & 0 \\ 0 & \mathbf{L}_2 & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathbf{L}_k \end{bmatrix} \) and \( \mathbf{L}_k = \text{diag}(l_{k1}, \ldots, l_{kn}) \) is a \( n \times n \) matrix with \( l_{ki} = \)

\[
\left\{ g'(g^{-1}(\mathbf{X}_k^T \hat{\theta}_k)) a(\hat{\phi}_k)b'(\hat{\psi}_k) \right\} \left\{ \frac{\partial g^{-1}(\mathbf{y})}{\partial \mathbf{y}} \right\}_{\mathbf{y} = \mathbf{x}_i^T \beta} \text{ for } k = 1, \ldots, K, \ i = 1, \ldots, n ; \ \mathbf{X}^* = \left[ \begin{array}{cccc} \mathbf{X}_{j\text{diag}} & 0 & \cdots & 0 \\ 0 & \mathbf{X}_{j\text{diag}} & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathbf{X}_{j\text{diag}} \end{array} \right], \ \mathbf{X}_{j\text{diag}} = \text{diag}(X_{1j}, \ldots, X_{nj}) \text{ is a } n \times n \text{ matrix for } j = 1, \ldots, p.
\]

Therefore, for each \( j \), the second summation is given by \( \mathbf{r}^T \mathbf{X}_{\text{Abdiag}} \mathbf{C} \mathbf{X}_{\text{Abdiag}}^T \mathbf{L} \mathbf{X}_{\text{rbind}}^* \mathbf{X}_{\text{rbind}} \), which can be rewritten as \( \mathbf{X}_{\text{rbind}}^T \mathbf{V} \mathbf{X}_{\text{rbind}} \), where \( \mathbf{V} = \text{diag}(v_1, \ldots, v_n) \) and \( v_i \) is the \( i \)th element of the row vector \( \mathbf{r}^T \mathbf{X}_{\text{Abdiag}} \mathbf{C} \mathbf{X}_{\text{Abdiag}}^T \mathbf{L} \). Plugging these expressions in (4), we get

\[
\mathbf{J}_n(\beta) = \mathbf{X}_{\text{rbind}}^T (\mathbf{W} \mathbf{X}_{\text{Abdiag}} \mathbf{C} \mathbf{X}_{\text{Abdiag}}^T \mathbf{W} + \mathbf{V}) \mathbf{X}_{\text{rbind}}, \quad (21)
\]

where \( \mathbf{W} \) and \( \mathbf{V} \) are diagonal matrices. Note that \( \mathbf{W} \) is a positive definite matrix when the link function is identity or logit since the diagonal elements are all ones or positive, respectively. Let \( \mathbf{W}^* = \mathbf{W} \mathbf{X}_{\text{Abdiag}} \mathbf{C} \mathbf{X}_{\text{Abdiag}}^T \mathbf{W} + \mathbf{V} \). Then, plugging in the expressions from (19) and (21) to (18), we get the \( t \)th iteration step

\[
\beta^{(t+1)} = \beta^{(t)} - [\mathbf{X}_{\text{rbind}} \mathbf{W}^* \mathbf{X}_{\text{rbind}}]^{-1} \mathbf{X}_{\text{rbind}}^T \mathbf{W} \mathbf{X}_{\text{Abdiag}} \mathbf{C} \mathbf{X}_{\text{Abdiag}}^T \mathbf{r}.
\]

Case II: \( \phi \) is unknown

When \( \phi \) is unknown, we have an additional moment function for \( \phi \), which is given by

\[
s(\phi_k) = - (Y_i \hat{\psi}_k - b(\hat{\psi}_k)) \frac{a'(\phi_k)}{a^2(\phi_k)} + c'(Y_i; \phi_k).
\]

Then,

\[
E_{Y_i|X_i}(s(\phi_k)) = - \left\{ g^{-1}(\mathbf{x}_i^T \beta) \hat{\psi}_k - b(\hat{\psi}_k) \right\} \frac{a'(\phi_k)}{a^2(\phi_k)} + E_{Y_i|X_i}\left\{ c'(Y_i; \phi_k) \right\}.
\]

Note that the first summand does not depend on \( \phi \), but the second one does since the distribution of \( Y_i|X_i \) depends on \( \phi_k \). Hence, we denote the second summand by \( q_{ki}(\phi) \). Then, the above equation becomes

\[
E_{Y_i|X_i}(s(\phi_k)) = - \left\{ g^{-1}(\mathbf{x}_i^T \beta) \hat{\psi}_k - b(\hat{\psi}_k) \right\} \frac{a'(\phi_k)}{a^2(\phi_k)} + q_{ki}(\phi).
\]

After plugging in the estimates of dispersion parameters, \( \hat{\phi}_k \)'s, and the variance functions, \( b(\hat{\psi}_k) \)'s, we have the following moment vector for \( \phi \):

\[
\mathbf{U}_n(\phi) = \left( \frac{1}{n} \sum_{i=1}^n u_{1i} \ldots \frac{1}{n} \sum_{i=1}^n u_{Ki} \right)^T,
\]

where \( u_{ki}(\phi) = \frac{(b(\hat{\psi}_k) - g^{-1}(\mathbf{x}_k^T \beta) \hat{\psi}_k) a' (\phi_k)}{a^2 (\phi_k)} + q_{ki}(\phi) \) and \( q_{ki}(\phi) = E_{Y_i|X_i} \frac{\partial c(Y_i, \phi_k)}{\partial \phi_k} |_{\phi_k = \hat{\phi}_k} \) for each \( k \) and \( i \).

Similar to Case I, but much easier in algebraic calculations, we use the GMM method to minimize \( \mathbf{U}_n(\phi)^T \mathbf{C} \mathbf{U}_n(\phi) \) and have the following \( t \)th iteration step of the NR algorithm:

\[
\phi^{(t+1)} = \phi^{(t)} - J_n^{-1}(\phi^{(t)})(D_n(\phi^{(t)})),
\]
where
\[
D_n(\phi) = \frac{\partial}{\partial \phi} \{ U_n^T(\phi) C U_n(\phi) \} = 2U_n^T(\phi) C \frac{\partial}{\partial \phi} q_n(\phi),
\]
\[
J_n(\phi) = \frac{\partial^2}{\partial \phi^2} \{ U_n^T(\phi) C U_n(\phi) \} = \frac{\partial}{\partial \phi} D_n(\phi)
= 2 \left\{ U_n^T(\phi) C \frac{\partial^2 q_n(\phi)}{\partial \phi^2} + \left( \frac{\partial q_n(\phi)}{\partial \phi} \right)^T C \frac{\partial}{\partial \phi} q_n(\phi) \right\},
\]
and \( q_n = \left( \frac{1}{n} \sum_{i=1}^{n} q_{1i}(\phi) \right) \ldots \left( \frac{1}{n} \sum_{i=1}^{n} q_{Ki}(\phi) \right)^T \). Therefore, the \( t \)th step of NR algorithm can be written as
\[
\phi(t+1) = \phi(t) - J_n^{-1}(\phi(t)) \left( U_n^T(\phi(t)) C \frac{\partial q_n(\phi)}{\partial \phi} \right|_{\phi=\phi(t)}.\]

C  Full Proof of Theorem 1 and Checking Regularity Assumptions in Two Examples

We first provide a complete proof of Theorem 1 and then check the assumptions for logistic and linear regression models.

Proof of Theorem 1. First, we show the consistency of \( \hat{\beta} \). Denote \( \hat{\theta} \) and \( \theta^* \) as stacked vectors of \( \hat{\theta}_k \)'s and \( \theta_k^* \)'s, respectively. Denote \( U_0(\hat{\beta}, \hat{\theta}) = EU(X; \beta, \theta) \) and \( Q_0(\beta) = U_0(\beta, \theta^*)^T C U_0(\beta, \theta^*) \).

By (A1) and Lemma 2.3 of Newey and McFadden (1994), \( Q_0(\beta) \) is uniquely minimized at \( \theta^* \).

By (A2), (A3), (A4) and Lemma 2.4 of Newey and McFadden (1994), \( U_0(\beta, \theta) \) is continuous and \( U_n(\beta, \theta) \) converges uniformly to \( U_0(\beta, \theta) \) for \( (\beta, \theta) \in D_\beta \times N_c(\theta^*) \), where \( N_c(\theta^*) \) is a compact subset of \( N(\theta^*) \) including \( \theta^* \). Note that \( \hat{\theta} \) is a consistent estimator of \( \theta^* \). With probability going to one (wpg1),
\[
\sup_{\beta \in D_\beta} ||U_n(\beta, \hat{\theta}) - U_0(\beta, \hat{\theta})|| \leq \sup_{(\beta, \theta) \in D_\beta \times N_c(\theta^*)} ||U_n(\beta, \theta) - U_0(\beta, \theta)||.
\]

Then, \( U_n(\beta, \hat{\theta}) - U_0(\beta, \hat{\theta}) \) converges uniformly in probability to 0 for \( \beta \in D_\beta \).

Note that, for any \( r > 0 \), wpg1,
\[
\sup_{\beta \in D_\beta} ||U_0(\beta, \hat{\theta}) - U_0(\beta, \theta^*)|| \leq \sup_{\beta \in D_\beta} \mathbb{E} \sup_{\theta^* \in \theta^*} ||U(\beta, \theta) - U(\beta, \theta^*)||.
\]

By (A3), (A4) and Dominant Convergence Theorem, \( \mathbb{E} \sup_{||\theta - \theta^*|| < r} ||U(\beta, \theta) - U(\beta, \theta^*)|| \) converges to 0 for every \( \beta \in D_\beta \) as \( r \) decreases to 0. Note that \( \mathbb{E} \sup_{||\theta - \theta^*|| < r} ||U(\beta, \theta) - U(\beta, \theta^*)|| \) decreases as \( r \) decreases for each \( \beta \). By (A2) and Dini’s Theorem (see, for example, Theorem 7.13 of Rudin (1976)), \( \mathbb{E} \sup_{||\theta - \theta^*|| < r} ||U(\beta, \theta) - U(\beta, \theta^*)|| \) converges uniformly in probability to 0 for \( \beta \in D_\beta \) as \( r \) decreases to 0. Then, \( U_0(\beta, \hat{\theta}) - U_0(\beta, \theta^*) \) converges uniformly in probability to 0 for \( \beta \in D_\beta \).

By combining the above two results, it follows that \( U_n(\beta, \hat{\theta}) \) converges uniformly in probability to \( U_0(\beta, \theta^*) \) for \( \beta \in D_\beta \).

By the triangle and Cauchy-Schwartz inequalities,
\[
\sup_{\beta \in D_\beta} ||Q_n(\beta) - Q_0(\beta)|| \leq ||\hat{C}|| \sup_{\beta \in D_\beta} ||U_n(\beta, \hat{\theta}) - U_0(\beta, \theta^*)||^2
+ 2||\hat{C}|| \sup_{\beta \in D_\beta} ||U_0(\beta, \theta^*)|| \sup_{\beta \in D_\beta} ||U_n(\beta, \hat{\theta}) - U_0(\beta, \theta^*)||
+ ||\hat{C} - C|| \sup_{\beta \in D_\beta} ||U_0(\beta, \theta^*)||^2.
\]
Since \( \hat{C} \) is a consistent estimator of \( C \), \( ||\hat{C}|| \) converges in probability to \( ||C|| \), which is finite; \( ||C - \hat{C}|| \) converges in probability to 0. Since \( U_0(\beta, \theta^*) \) is continuous for \( \beta \in D_\beta \) and \( D_\beta \) is compact, \( \sup_{\beta \in D_\beta} ||U_0(\beta, \theta^*)||^2 \) is finite. Since \( \sup_{\beta \in D_\beta} ||U_0(\beta, \theta) - U_0(\beta, \theta^*)||^2 \) converges in probability to 0, \( \sup_{\beta \in D_\beta} ||U_n(\beta, \hat{\theta}) - U_n(\beta, \theta^*)||^2 \) converges in probability to 0. Thus, \( Q_n(\beta) - Q_0(\beta) \) converges uniformly in probability to 0 for \( \beta \in D_\beta \). Recall that \( \beta^* \) is the unique minimizer of \( Q_0(\beta) \). By Theorem 2.1 of Newey and McFadden (1994), \( \hat{\beta} \) is a consistent estimator of \( \beta^* \).

Next, we derive the asymptotic distribution of the GMeta estimator \( \hat{\beta} \). Note that \( \hat{\beta} \) is a solution to

\[
G_n(\beta, \hat{\theta})^T \hat{C} U_n(\beta, \hat{\theta}) = 0,
\]

where \( G_n(\beta, \hat{\theta}) = \frac{\partial}{\partial \beta} U_n(\beta, \hat{\theta}) \), the Jacobian of \( U_n(\beta, \hat{\theta}) \). On the other hand, by the Mean Value Theorem,

\[
U_n(\beta, \hat{\theta}) = U_n(\beta^*, \hat{\theta}) + G_n(\beta, \hat{\theta})(\hat{\beta} - \beta^*),
\]

where \( \beta \) denotes a matrix each column of which corresponds to each element of \( U_n(\beta, \hat{\theta}) \). After left multiplying \( G_n(\beta, \hat{\theta})^T \hat{C} \) to the above identity, it follows

\[
\sqrt{n}(\hat{\beta} - \beta^*) = -M_n \sqrt{n} U_n(\beta^*, \hat{\theta}),
\]

where \( M_n = [G_n(\beta, \hat{\theta})^T \hat{C} G_n(\beta, \hat{\theta})]^{-1} G_n(\beta, \hat{\theta})^T \hat{C} \).

Consider \( M_n \). Since \( \beta \) is a consistent estimator of \( \beta^* \), each column of \( \hat{\beta} \) is a consistent estimator of \( \beta^* \). On the other hand, \( \hat{\theta} \) is a consistent estimator of \( \theta^* \). By (A5), (A6) and Lemma 2.4 of Newey and McFadden (1994), \( G_n(\beta, \theta) \) converge uniformly to continuous \( \mathbb{E} \frac{\partial}{\partial \beta} U(X; \beta, \theta) \) for \((\beta, \theta) \in D_\beta \times N_\varepsilon(\theta^*) \), where \( N_\varepsilon(\theta^*) \) is a compact subset of \( N(\theta^*) \), including \( \theta^* \). Since \( \hat{\beta} \) and each column of \( \beta \) converge in probability to \( \beta^* \) and \( \hat{\theta} \) is a consistent estimator of \( \theta^* \), by, for example, Theorem 9.4 of Keener (2010), both \( G_n(\beta, \hat{\theta}) \) and \( G_n(\beta, \hat{\theta}) \) converge in probability to \( \Gamma = \mathbb{E} \frac{\partial}{\partial \beta} U(X; \beta^*, \theta^*) \). Thus, by noting \( \hat{C} \xrightarrow{P} C \), \( M_n \) converges in probability to \( (\Gamma^T \Gamma)^{-1} \Gamma^T C \).

Consider \( \sqrt{n} U_n(\beta^*, \hat{\theta}) \). By the Mean Value Theorem,

\[
U_n(\beta^*, \hat{\theta}) = U_n(\beta^*, \theta^*) + V_n(\beta^*, \hat{\theta})(\hat{\theta} - \theta^*),
\]

where \( V_n \) is the Jacobian of \( U_n(\beta^*, \theta) \) as a function of \( \theta \) and \( \hat{\theta} \) is a matrix each column of which corresponds to each element of \( U_n(\beta^*, \theta) \). Thus,

\[
\sqrt{n} U_n(\beta^*, \hat{\theta}) = \sqrt{n} U_n(\beta^*, \theta^*) + V_n(\beta^*, \hat{\theta}) \sqrt{n}(\hat{\theta} - \theta^*).
\]

By (A9) and Central Limit Theorem, \( \sqrt{n} U_n(\beta^*, \theta^*) \xrightarrow{d} N(0, \Delta) \). Since \( \hat{\theta} \) is a consistent estimator of \( \theta^* \), each column of \( \hat{\theta} \) converges in probability to \( \theta^* \). Similar to the above argument, by (A7), (A8), Lemma 2.4 of Newey and McFadden (1994) and Theorem 9.4 of Keener (2010),

\[
V_n(\beta^*, \hat{\theta}) \xrightarrow{P} \text{diag}(W_1, W_2, \ldots, W_K),
\]

where, for \( k = 1, 2, \ldots, K \), \( W_k = \mathbb{E} \frac{\partial}{\partial \theta^*_k} u_k(X, \beta^*, \theta_k) \big|_{\theta_k = \theta^*_k} \). Note that the \( K \) study data sets are independent. So are \( \hat{\theta}_k \)’s. Note that \( n_k/n \to c_k \), where \( c_k \) is a positive constant for \( k = 1, 2, \ldots, K \). Then \( \sqrt{n}(\hat{\theta} - \theta^*) \) converges in distribution to

\[
N(0, \text{diag}((1/c_1)\Sigma_1, (1/c_2)\Sigma_2, \ldots, (1/c_K)\Sigma_K))\).
Since the $K$ data sets and the reference data are independent, the above results imply that
\( \sqrt{n}U_n(\beta^*, \hat{\theta}) \) converges in distribution to $N(0, \Delta + \Lambda)$, where $\Lambda$ is a block diagonal matrix whose $k$th block is $(1/c_k)W_k\Sigma_kW_k^T$ for $k = 1 : K$.

Therefore, with the above two results on $M_n$ and $\sqrt{n}U_n(\beta^*, \hat{\theta})$ and by Slutsky’s theorem, the asymptotic normality of $\sqrt{n}(\hat{\beta} - \beta^*)$ follows.

\[\text{Example 1 (Check Assumptions for Logistic Regression Model).}\] Suppose the maximal model is

\[Y | \mathbf{X} \sim \text{Bernoulli}(\frac{1}{1 + \exp(-\mathbf{X}^T \beta^*)}), \]

where $\mathbf{X} = (1, \mathbf{X}^T)^T$, $\mathbf{X} = (X_1, \cdots, X_d)^T$ is the vector of covariates and $\beta^* = (\beta_0^*, \beta_1^*, \cdots, \beta_p^*)^T$ is the vector of coefficients of interest. There are $K$ independent studies and the reduced model of the $k$th study is given by

\[Y | \mathbf{X}_{A_k} \sim \text{Bernoulli}(\frac{1}{1 + \exp(-\mathbf{X}_{A_k}^T \theta_k)}), \]

where $\mathbf{X}_{A_k} = (1, \mathbf{X}_{A_k}^T)^T$, $\mathbf{X}_{A_k}$ is a sub-vector of $\mathbf{X}$ with $A \subset \{1, 2, \cdots, p\}$. For example, $\mathbf{X}_A = (X_1, X_2)^T$ when $A = \{1, 2\}$.

The global identification assumption (A1) usually holds and $D_\beta$ is a compact set. Next, we check the assumptions (A3) to (A9). The moment functions from the $k$th study is given by

\[u_k(\mathbf{X}; \beta, \theta_k) = [\frac{1}{1 + e^{-\mathbf{X}_k^T \beta}} - \frac{1}{1 + e^{-\mathbf{X}_{A_k}^T \theta_k}}] \mathbf{X}_{A_k}. \]

It is a continuous function of $\beta$ and $\theta_k$. Then, (A3) is satisfied. Note that

\[\sup_{(\beta, \theta) \in D_\beta \times N(\theta^*)} \left| \left| \frac{1}{1 + e^{-\mathbf{X}_k^T \beta}} - \frac{1}{1 + e^{-\mathbf{X}_{A_k}^T \theta_k}} \right| \mathbf{X}_{A_k} \right| \leq 2 \| \mathbf{X} \|_1, \]

where $\| \cdot \|$ and $\| \cdot \|_1$ are the $l_2$ and $l_1$ norms, respectively. Then, given $\mathbb{E}|X_i| < \infty$ for each $i$, (A4) is satisfied. Note that

\[\frac{\partial}{\partial \beta} u_k(\mathbf{X}; \beta, \theta_k) = \frac{e^{-\mathbf{X}_k^T \beta}}{(1 + e^{-\mathbf{X}_k^T \beta})^2} \mathbf{X}_{A_k} \mathbf{X}^T, \quad (22)\]

which does not depend on $\theta_k$ and is continuous for each $\beta$. Then, (A5) is verified. Note that

\[\sup_{(\beta, \theta) \in D_\beta \times N(\theta^*)} \left| \frac{e^{-\mathbf{X}_k^T \beta}}{(1 + e^{-\mathbf{X}_k^T \beta})^2} \right| \mathbf{X}_{A_k} \mathbf{X}^T \leq \| \mathbf{X} \| \mathbf{X}^T \|_1. \]

Given $\mathbb{E}X_i^2 < \infty$ for each $i$, (A6) is satisfied. Note that

\[\frac{\partial}{\partial \theta_k} u_k(\mathbf{X}; \beta^*, \theta_k) = -\frac{e^{-\mathbf{X}_{A_k}^T \theta_k}}{(1 + e^{-\mathbf{X}_{A_k}^T \theta_k})^2} \mathbf{X}_{A_k} \mathbf{X}^T, \]

which is continuous for each $\theta_k$. Then, (A7) is satisfied. Note that

\[\sup_{(\beta, \theta) \in D_\beta \times N(\theta^*)} \left| -\frac{e^{-\mathbf{X}_{A_k}^T \theta_k}}{(1 + e^{-\mathbf{X}_{A_k}^T \theta_k})^2} \mathbf{X}_{A_k} \mathbf{X}^T \right| \leq \| \mathbf{X} \| \mathbf{X}^T \|_1. \]
Given $\mathbb{E}X_i^2 < \infty$ for each $i$, (A8) is satisfied. The absolute value of each element of $\Delta(\beta^*, \theta^*)$ is less than 1, $\mathbb{E}|X_i|$ or $\mathbb{E}|X_iX_j|$ for each $i$ and $j$. Given $\mathbb{E}X_i^2 < \infty$, $\Delta(\beta^*, \theta^*)$ is finite. Note that $\Gamma(\beta^*, \theta_k^*)$ is a stacked matrix of (22) for $k = 1 : K$. Given each covariate of the maximal model is in at least one reduced model and $\mathbb{E}[e^{-X^T\beta}/(1+e^{-X^T\beta})^2]XX^T$ is positive definite, $\Gamma(\beta^*, \theta^*)$ is of full rank. Then, (A9) is verified.

**Example 2** (Check Assumptions for Linear Regression Model). Suppose the true maximal model is

$$Y|X \sim N(X^T \beta^*, \sigma^{*2}),$$

where $X = (X_1, X_2, \cdots, X_p)^T$; $\beta^* = (\beta_1^*, \beta_2^*,\cdots, \beta_p^*)^T$; $\mathbb{E}X = 0$ and $\mathbb{E}Y = 0$, that is, both $X$ and $Y$ are centered. There are $K$ independent studies and the reduced model of the $k$th study is given by

$$Y|X_{A_k} \sim N(X_{A_k}^T \theta_k, \sigma_k^2).$$

For simplicity, assume $\sigma^{*2}$ is known and the unknown parameter is $\beta^*$. The case with unknown $\sigma^{*2}$ can be similarly considered.

The moment functions from the $k$th reduced model is given by

$$u_k(X; \beta; \theta_k, \sigma_k^2) = \frac{1}{\sigma_k^2} [X_{A_k} X^T \beta - X_{A_k} X_{A_k}^T \theta_k],$$

which is linear in $\beta$. Note that

$$\frac{\partial}{\partial \beta} u_k(X; \beta; \theta_k, \sigma_k^2) = \frac{1}{\sigma_k^2} X_{A_k} X^T. \quad (23)$$

Given each covariate of the maximal model is in at least one reduced model and $\mathbb{E}XX^T$ is positive definite, $\Gamma(\beta^*, \theta_k^*, \sigma_k^{*2}) = \frac{\partial}{\partial \beta} u_k(X; \beta^*; \theta_k^*, \sigma_k^{*2})$ is of full rank. Given $C$ is positive definite, (A1) is satisfied. Suppose $D_\beta$ is a compact set. Then (A2) is satisfied.

Next, we check the assumptions (A3) to (A9). Note that $u_k(X; \beta; \theta_k, \sigma_k^2)$ is continuous for every $(\beta, \theta_k, \sigma_k^2)$. Then, (A3) is satisfied. Note that

$$\sup_{(\beta, \theta_k, \sigma_k^2)} \|\frac{1}{\sigma_k^2} [X_{A_k} X^T \beta - X_{A_k} X_{A_k}^T \theta_k]\| \leq \frac{1}{\sigma_k^2} \|\beta\| + \|\theta_k\| \|XX^T\|_1,$$

Denote a finite upper bound of $\|\beta\|$ for $\beta \in D_\beta$ as $C(\beta)$, a finite upper bound of $\|\theta_k\|$ for $\theta_k \in N(\theta_k^*)$ as $C(\theta_k)$, and a positive finite lower bound of $\sigma_k^2$ for $\sigma_k^2 \in N(\sigma_k^{*2})$ as $\sigma_L^2$. The supremum of $(1/\sigma_k^2)(\|\beta\| + \|\theta_k\|)$ for $(\beta, \theta_k, \sigma_k^2) \in D_\beta \times N(\theta_k^*) \times N(\sigma_k^{*2})$ is bounded by $(1/\sigma_L^2)(C(\beta) + C(\theta_k))$. Given $\mathbb{E}X_i^2 < \infty$ for each $i$, (A4) is satisfied. Note that $\frac{\partial}{\partial \sigma_k^2} u_k(X; \beta; \theta_k, \sigma_k^2)$ does not depend on $\beta$ and $\theta_k$ and is continuous for each $\sigma_k^2$. Then, (A5) is satisfied. Note that

$$\sup_{\sigma_k^{*2} \in N(\sigma_k^{*2})} \|\frac{1}{\sigma_k^2} [X_{A_k} X^T]\| \leq \frac{1}{\sigma_L^2} \|XX^T\|_1.$$

Given $\mathbb{E}X_i^2 < \infty$ for each $i$, (A6) is satisfied. Note that

$$\frac{\partial}{\partial (\theta_k, \sigma_k^2)} u_k(X; \beta; \theta_k, \sigma_k^2) = (\frac{1}{\sigma_k^2} X_{A_k} X_{A_k}^T, -\frac{1}{\sigma_k^2} [X_{A_k} X^T \beta - X_{A_k} X_{A_k}^T \theta_k]),$$
which is continuous for every \((\beta, \theta_k, \sigma_k^2)\). Then, \((A7)\) is satisfied. For every \((\beta, \theta_k, \sigma_k^2) \in D_{\beta} \times N(\theta_k^*, N(\sigma_k^{*2}))\), the \(l_2\) norm of the above partial derivative is less than or equal to
\[
\frac{1}{\sigma^2_L} + \frac{1}{\sigma^4_L} (C(\beta) + C(\theta_k)) ||XX^T||_1.
\]

Given \(\mathbb{E}X_i^2 < \infty\) for each \(i\), \((A8)\) is satisfied. Each element of \(\Delta(\beta^*, \{\theta^*_k\}, \{\sigma^{*2}_k\})\) is equal to a constant times \(\mathbb{E}X_{i_1}X_{i_2}X_{i_3}X_{i_4}\) for some \(i_1, i_2, i_3, i_4\). Given \(\mathbb{E}X_i^4 < \infty\) for each \(i\), \(\Delta\) is finite. Note that \(\Gamma(\beta^*, \{\theta^*_k\}, \{\sigma^{*2}_k\})\) is a stacked matrix of \((23)\) for \(k = 1 : K\). As in checking \((A2)\), given each covariate of the maximal model is in at least one reduced model and \(\mathbb{E}XX^T\) is positive definite, \(\Gamma\) is of full rank. Then, \((A9)\) is verified. \(\square\)