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Meta-analysis methods and models with applications in evaluation of cholesterol-lowering drugs

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Abstract

In this paper, we propose a class of multivariate random effects models allowing for the inclusion of study-level covariates to carry out meta-analyses. As existing algorithms for computing maximum likelihood estimates often converge poorly or may not converge at all when the random effects are multi-dimensional, we develop an efficient expectation–maximization algorithm for fitting multi-dimensional random effects regression models. In addition, we also develop a new methodology for carrying out variable selection with study-level covariates. We examine the performance of the proposed methodology via a simulation study. We apply the proposed methodology to analyze metadata from 26 studies involving statins as a monotherapy and in combination with ezetimibe. In particular, we compare the low-density lipoprotein cholesterol-lowering efficacy of monotherapy and combination therapy on two patient populations (naïve and non-naïve patients to statin monotherapy at baseline), controlling for aggregate covariates. The proposed methodology is quite general and can be applied in any meta-analysis setting for a wide range of scientific applications and therefore offers new analytic methods of clinical importance.

Keywords

aggregate covariates; heterogeneity; normal meta-regression models; multiple trials; random effects; variable selection

1. Introduction

An estimated 12 million Americans are taking cholesterol-lowering drugs, and experts are recommending that another 23 million should be taking them. The National Cholesterol Education Program has issued treatment guidelines identifying low-density lipoprotein cholesterol (LDL-C, ‘bad’ cholesterol) as a causative factor for coronary heart disease and as the main target for cholesterol-lowering and lipid-lowering therapy. Cholesterol-lowering medicines called ‘statins’ work mainly in the liver to decrease the production of cholesterol and reduce cholesterol in the bloodstream. This class of drugs includes: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), rosuvastatin (Crestor), pravastatin (Pravachol), and fluvastatin (Lescol). On the other hand, a drug called ezetimibe (Zetia) works in the digestive tract. It is unique in the way it helps block absorption of cholesterol

that comes from food. Ezetimibe (EZE) can complement statins in targeting both sources of cholesterol.

In general, statins positively affect the lipid profile by increasing high-density lipoprotein cholesterol (HDL-C, 'good' cholesterol) and decreasing LDL-C and triglycerides (TG). Clinical studies have shown that statins significantly reduce the risk of heart attack and death in patients with coronary artery disease and can also reduce cardiac events in patients with high cholesterol levels. Statins are the first-line treatment in most patients, but lipid goals are frequently not achieved because of inadequate response to therapy, poor compliance, or concerns regarding the increased potential for side effects at higher doses. EZE can be given as monotherapy to lower cholesterol levels in patients who are intolerant to statin or in whom treatment with statin is not appropriate. EZE can also be used in combination with a statin in patients whose cholesterol levels remain elevated despite treatment with statin alone. It can be either co-administered with the statin dose or given as a fixed-dose combination tablet (known as Vytorin) containing EZE and simvastatin.

There has been a rich literature on statistical methods using random effects models for meta-analysis for the past 20 years. Now, random effects modeling for meta-analysis has become well accepted (e.g., [1–12]). A number of meta-analyses investigating efficacy and safety of various statins have been reported in the literature over the last 5 years. See, for example, [13, 14], the Cholesterol Treatment Trialists Collaboration Group [15], and [16]. There have been also meta-analyses reported in the literature comparing safety and efficacy of monotherapy with statins versus combination therapy of EZE added to statins (coadministration or combination tablet). Mikhailidis *et al.* [17] performed a meta-analysis to investigate the cholesterol-lowering effect of EZE added to ongoing statin therapy. Another meta-analysis involving 14 clinical trials was done by Catapano *et al.* [18] to investigate the lipid-altering efficacy of EZE co-administered with simvastatin compared with Rosuvastatin.

Common features of the meta-analyses cited previously are a lack of incorporation of (or adjusting for) any covariates through modeling and the lack of accommodating and assessing several types of treatments across studies. Also, most of the meta-analyses conducted in the literature are for adverse event comparisons, and such analyses use outcome measures of either odds ratios or relative risks. An outcome measure of mean difference is frequently used for efficacy comparisons, which is our primary analysis and outcome measure in this paper. While carrying out a meta-analysis, it is crucial to account for and understand differences among the studies to be combined with respect to study design, duration of treatment, durations of follow-up, and patient population, which is a function of entry criteria. As can be seen from Tables I–III, the treatment arms, treatment durations, and patient entry criteria for the studies considered here varied considerably, warranting inclusion of covariates into the model. The study-level aggregate estimates available from individual publications (listed in Tables I and II) and used in the meta-analysis here were indeed adjusted for selected covariates, but the set of selected covariates varied from study to study. Thus, the available aggregate estimates were not uniformly adjusted and again warrant the inclusion of important covariates in the meta-analysis.

There are some recent developments on meta-regression models. See, for example, [19–26]. Compared with the current literature on meta-regression, our contributions in this paper are several-fold. First, we develop novel meta-analysis models on the basis of multi-dimensional random effects that allow for study-level covariates and general covariance matrices for the random effects. Next, we develop an efficient expectation–maximization (EM) algorithm for fitting these models and develop methods for examining heterogeneity and variable selection for these models. Specifically, for assessing heterogeneity, we generalize Cochran's Q

statistic [27] to meta-analysis regression models with covariates and multi-dimensional random effects in order to test homogeneity among studies. Finally, we have assembled a dataset on the basis of 26 large clinical studies and have applied the proposed methods to this dataset in order to address some important clinical questions. We organize the rest of this paper as follows. In Section 2, we give a detailed description of the LDL-C data on the basis of the 26 studies and discuss the specific hypotheses of interest for these studies. In Section 3, we give the full development of the meta-analysis regression models with multi-dimensional random effects in Section 3.1, present an extension of Cochran's Q in Section 3.2, and provide the necessary mathematical formulation of three variable selection criteria in Section 3.3, respectively. In Section 4, we carry out an extensive simulation study to examine the performance of the proposed methods. Section 5 presents a detailed analysis of the LDL-C data, and we conclude the paper with some discussion and extensions of the proposed methodology in Section 6. The detailed development of the EM algorithm including closed-form expressions for the E-step and the estimates in the M-step is given in the Appendix.

2. Low-density lipoprotein cholesterol data

In this paper, we carry out aggregate data meta-analyses to evaluate the LDL-C lowering effect of EZE in combination with statin in comparison with statin alone in randomized controlled trials on treatment-naïve patients at baseline (on a first-line therapy) and those continuing on statins at baseline (on a second-line therapy). The objective is to evaluate the LDL-C lowering effect of EZE added to statin versus statin in treatment-naïve patients or EZE added to baseline statin versus placebo added to baseline statin in statin-treated patients. The study inclusion criteria were Merck-sponsored double-blind, randomized, active or placebo-controlled clinical trials on adult patients with primary hypercholesterolemia.

These criteria led to 26 studies whose titles, treatment groups, treatment durations, number of patients, and the citations of primary publications are given in Table I for the first-line therapy studies and Table II for the second-line therapy studies. These trials were conducted between November 1999 and October 2008, and study durations ranged from 4 to 24 weeks. Some trials had longer durations with titration of doses, but only the data prior to the first titration were used in the analyses. The primary end point in these trials was the percent reduction in LDL-C from baseline. The entry criteria for the patients in each of these studies are summarized in Table III. Figure 1 shows the forest plots of the metadata for these 26 studies. Note that the reported means were model-based means. In practice, the patient-level data are not available to the researchers, and hence our focus here is on aggregate data meta-analysis instead of patient-level data meta-analysis.

For the analyses, different statins and their doses are combined to form the statin and (statin + EZE) treatment groups. EZE is available at only one dose of 10 mg, and the statins used in these studies included simvastatin, atorvastatin, lovastatin, rosuvastatin, pravastatin, and fluvastatin. The following hypotheses are of interest: H_{01} : No treatment differences (addition of EZE has no effect) with respect to LDL-C lowering (percent reduction) in the first-line therapy studies; H_{02} : No treatment differences (addition of EZE has no effect) with respect to LDL-C lowering (percent reduction) in the second-line therapy studies; and H_{03} : Treatment differences within the first-line and second-line therapy studies are the same.

3. Methods for meta-analysis with multi-dimensional random effects and aggregate covariates

3.1. The meta-analysis regression model

Consider K randomized trials (studies), where each trial has J treatment arms, and patients in each trial are either all on the first-line therapy or the second-line therapy prior to the trial. Let y_{jk} denote the aggregate response with a *known* precision parameter w_{jk} . Let I_k be the indicator function such that $I_k = 1$ if patients are on the second-line therapy and $I_k = 0$ if patients are on the first-line therapy. Also let $\mathbf{x}_{jk}$ denote a p -dimensional vector of aggregate covariates for $j = 1, 2, \dots, J$ and $k = 1, 2, \dots, K$. Then, we propose the following normal random effects model for the meta-analysis:

$$y_{jk} = \mathbf{x}_{jk}'\beta + (1 - I_k)\gamma_{1jk} + I_k\gamma_{2jk} + \varepsilon_{jk}, \quad (3.1)$$

where $\beta = (\beta_1, \beta_2, \dots, \beta_p)$ is the vector of fixed effects regression coefficients corresponding to the p aggregate covariates and

$$\varepsilon_{jk} \sim N(0, w_{jk}^{-1}), \quad (3.2)$$

independently, for $j = 1, 2, \dots, J$ and $k = 1, 2, \dots, K$. Let $\gamma_{R,1k} = (\gamma_{R,1k1}, \gamma_{R,1k2}, \dots, \gamma_{R,1kj})$, and $\gamma_{R,2k} = (\gamma_{R,2k1}, \gamma_{R,2k2}, \dots, \gamma_{R,2kj})$, which represent the vectors of random effects of the first-line and second-line therapies for the model. Thus, $\gamma_{R,k} = (\gamma_{R,1k}', \gamma_{R,2k}')'$ represents the vector of random effects for the model. We assume $\gamma_{R,1k}$ and $\gamma_{R,2k}$ are independent, and

$$\gamma_{R,\ell k} = \gamma_{\ell} + \xi_{\ell k}, \quad \xi_{\ell k} = (\xi_{\ell k1}, \dots, \xi_{\ell kJ})' \sim N_J(\mathbf{0}, V_{\ell}), \quad (3.3)$$

where $V = (V_{jj})$ is an unknown $J \times J$ covariance matrix and $\gamma_{\ell} = (\gamma_{\ell 1}, \dots, \gamma_{\ell J})$ denotes the vector of the overall treatment effects when patients were on the ℓ th line therapy for $\ell = 1, 2$.

Let $\xi_k = (\xi_{1k}', \xi_{2k}')'$ and $\gamma = (\gamma_1', \gamma_2')'$. Using (3.3), we have $\gamma_{R,k} = \gamma + \xi_k$ and $\xi_k \sim N_{2J}(\mathbf{0}, V)$, where $V = \text{diag}(V_1, V_2)$.

We have proposed here a very general class of meta-regression models that are suited for analyzing metadata from studies involving first-line and second-line therapies. Such studies are becoming quite prominent in diabetes, cardiovascular, and cancer clinical trials where patients received a prior therapy that is identical or nearly identical to the therapy for the current clinical trial. Such types of studies pose many new challenges in the meta-regression setting such as multivariate and correlated random effects that lead to potentially high dimensional variance components. The meta-analysis regression model defined by (3.1), (3.2), and (3.3) is very general, which can accommodate several treatments in first-line and second-line as well as a large number of covariates. However, the resulting model requires estimation of the covariance matrix of the random effects, denoted by V , which is a block diagonal matrix. Simultaneous estimation of (V, γ) is not trivial and requires a sophisticated and computationally intensive EM algorithm, which is developed in the Appendix.

3.2. Test of statistical homogeneity

The hypotheses for heterogeneity across K studies are $H_0: V = 0$ versus $H_1: V > 0$, where $V > 0$ denotes that V is a positive definite matrix. In this regard, we extend the Q test statistic

for homogeneity proposed by Cochran [27] to meta-analysis regression models with multivariate random effects. In (3.3), when $V = 0$, $R_1 = \dots = R_K = 0$, indicating that there is no heterogeneity across the K studies. As R_k in (3.3) is a q -dimensional vector of random effects, the classical Q function of Cochran [27] is not well defined. In this case, we propose the following extension of the Q test statistic:

$$Q_K = \sum_{k=1}^K \left(\mathbf{y}_k - X_k^* \hat{\theta} \right)' W_k \left(\mathbf{y}_k - X_k^* \hat{\theta} \right), \quad (3.4)$$

where $\hat{\theta} = \left(\sum_{k=1}^K X_k^{*'} W_k X_k^* \right)^{-1} \sum_{k=1}^K X_k^{*'} W_k \mathbf{y}_k$, $\mathbf{y}_k = (y_{1k}, \dots, y_{Jk})$, $W_k = \text{diag}(w_{1k}, \dots, w_{Jk})$, $X_k^* = (X_k, \mathbf{Z}_k)$ is a $J \times (p+2J)$ matrix, $X_k = (\mathbf{x}_{1k}, \dots, \mathbf{x}_{Jk})$ is a $J \times p$ matrix, $\mathbf{Z}_k = (\mathbf{z}_{1k}, \dots, \mathbf{z}_{Jk})$ is the $J \times 2J$ matrix, and $\mathbf{z}_{jk} = ((1 - I_k) \mathbf{e}_j', I_k \mathbf{e}_j')$, where $\mathbf{e}_j = (0, \dots, 1, \dots, 0)$ with a 1 in its j th component and 0 elsewhere, for $j = 1, \dots, J$. Similar to [27], we can show that under the hypothesis of homogeneity, $V = 0$, and assuming that the regression model is correct, $Q_K \sim \chi_{JK-2J-p}^2$. Thus, if the regression model is correct, a rejection of the null hypothesis implies that there is heterogeneity across the K studies. However, without knowledge of whether the regression model is correct, a rejection of the null hypothesis implies either heterogeneity or misspecification of the regression model.

3.3. Variable selection for meta-analysis regression models

Let $\boldsymbol{\phi} = (\boldsymbol{\varphi}, V^{-1})$, where $\boldsymbol{\varphi} = (\boldsymbol{\beta}, \boldsymbol{\gamma})$, denotes the collection of all the unknown parameters.

Write $\tilde{\mathbf{x}}_{jk} = (\mathbf{x}'_{jk}, \mathbf{z}'_{jk})'$ for $j = 1, \dots, J$ and $X_k = (\mathbf{x}_{1k}, \mathbf{x}_{2k})$. For the meta-regression model defined by (3.1), (3.2), and (3.3), the marginal distribution of $\mathbf{y}_k$ is analytically available. After some algebra, we obtain

$$f(\mathbf{y}_k | X_k, \mathbf{Z}_k, \boldsymbol{\phi}, V) = \frac{|W_k^{-1} + \mathbf{Z}_k V \mathbf{Z}_k'|^{-\frac{1}{2}}}{(2\pi)^{J/2}} \exp \left\{ -\frac{1}{2} (\mathbf{y}_k - X_k \boldsymbol{\phi})' (W_k^{-1} + \mathbf{Z}_k V \mathbf{Z}_k')^{-1} (\mathbf{y}_k - X_k \boldsymbol{\phi}) \right\}.$$

Thus, the observed-data log-likelihood is given by

$$\ell_{\text{obs}}(\eta) = -\frac{JK}{2} \log(2\pi) - \frac{1}{2} \sum_{k=1}^K \left\{ \log |W_k^{-1} + \mathbf{Z}_k V \mathbf{Z}_k'| + (\mathbf{y}_k - X_k \boldsymbol{\phi})' (W_k^{-1} + \mathbf{Z}_k V \mathbf{Z}_k')^{-1} (\mathbf{y}_k - X_k \boldsymbol{\phi}) \right\}.$$

We consider three variable selection criteria for selection of the covariates in our meta-regression model, namely, the Akaike information criterion (AIC), Bayesian information criterion (BIC), and a finite-sample corrected version of AIC (AICC). These criteria are computed as follows:

$$\text{AIC} = -2\ell_{\text{obs}}(\hat{\eta}) + 2q, \text{AICC} = -2\ell_{\text{obs}}(\hat{\eta}) + 2q(JK)/(JK - q - 1), \text{BIC} = -2\ell_{\text{obs}}(\hat{\eta}) + q \log(K),$$

where $\hat{\eta}$ is the MLE of η and $q = p + 2J + J(J+1)$ is the dimension of η . See [28] and [29] for additional details. We mention here that in our variable selection procedure, $\mathbf{Z}_k$ and V are always kept in every model and, therefore, are never candidates for selection. Our variable

selection procedure is only concerned with selecting the covariates $\mathbf{x}_{jk}$, that is, components of $\mathbf{x}$.

4. A simulation study

To examine the performance of the proposed method, we carry out a simulation study with $K = 26$ trials and four trial-level covariates. Among the 26 trials, 13 are the first-line therapy trials, and the remaining 13 are the second-line trials. Within each trial, two treatment arms ($J = 2$) are assumed. The sample sizes, n_{jk} , were chosen to be the same as those in the LDL-C data discussed in Section 2. The within-subject standard deviations were set to the values of the standard errors (SEs), SD_{jk} , estimated from the LDL-C data. We used the values of baseline LDL-C, baseline HDL-C, age in years, and duration in weeks from the LDL-C data for these four covariates. Then, we generated the simulated data from the nine meta-regression models defined by (3.1), (3.2), and (3.3) with various combinations of γ and V . Specifically, $\gamma_{11} = -52$, $\gamma_{12} - \gamma_{11} = -12$, $\gamma_{21} = -23$, and $\gamma_{22} - \gamma_{21} = -20$ were used in all the nine meta-regression models. To evaluate the performance of the model selection criteria, we considered three covariate models (C-Models), namely, C-Model I: $\gamma = (0.1, -0.7, 0.6, 1.0)$ (four covariates); C-Model II: $\gamma = (0.1, -0.7, 0.0, 1.0)$ (three covariates); and C-Model III: $\gamma = (0.1, 0.0, 0.0, 1.0)$ (two covariates), respectively. For each covariate model, we considered three different values of V (the covariance matrix of the random effects) such that $V = V_0$ (large between-study variability), $V = V_0/2$ (moderate between-study variability), and $V = V_0/10$ (small between-study variability), where $V_0 = \text{diag}(V_{01}, V_{02})$, $V_{01} = \begin{pmatrix} 36 & -12 \\ -12 & 11 \end{pmatrix}$ and $V_{02} = \begin{pmatrix} 18 & -16 \\ -16 & 22 \end{pmatrix}$. For each meta-regression model, we generated 1000 simulated data sets, and for each simulated dataset, we fit 16 models. AIC, AICC, and BIC were computed for all 16 models, whereas the estimates of the model parameters were computed, and the test of statistical homogeneity was performed only under the true model, which was used to generate the simulated data.

Let ϕ_j denote the j th component of ϕ . Also, let ϕ_{ij} and $\text{SE}(\phi_{ij})$ be the maximum likelihood estimate of ϕ_j and the SE of ϕ_{ij} from the i th simulated dataset for $i = 1, 2, \dots, 1000$. We

define the simulation estimate (EST) and the SE to be $\frac{1}{1000} \sum_{i=1}^{1000} \hat{\phi}_{ij}$ and $\frac{1}{1000} \sum_{i=1}^{1000} \text{SE}(\hat{\phi}_{ij})$.

We also define the root of the mean squared error (RMSE) as $\left[\frac{1}{1000} \sum_{i=1}^{1000} (\hat{\phi}_{ij} - \phi_j^*)^2 \right]^{1/2}$, where ϕ_j^* is the true value of ϕ_j . Table IV shows ESTs, SEs, RMSEs, and powers of γ and V under the nine combinations of γ and V , where the power was calculated on the basis of a significance level of 0.05. From Table IV, we see that for all parameters, the ESTs were very close to the corresponding true values, and the SE and RMSE become smaller and the power increases when the number of covariates is less or there is less between-study variability. In particular, under C-Model III, the parameter estimates were quite accurate and had good powers given that the number of trials ($K = 26$) is relatively small. We notice that under C-Models I and II, when V is large, the estimate of γ_{21} has much lower power than that of γ_{11} , which is expected as the effect size of γ_{21} is much smaller than the one of γ_{11} . In addition, we computed the coverage probability (CP) of the 95% confidence interval on the basis of a normal approximation. The respective CPs for $(\gamma_{12}^* = \gamma_{12} - \gamma_{11}, \gamma_{22}^* = \gamma_{22} - \gamma_{21})$ in the 1000 simulations when $V = V_0, V_0/2$, and $V_0/10$ were (92.3%, 93.4%), (91.6%, 93.5%), and (92.4%, 95.0%) under C-Model I; (92.9%, 93.2%), (91.7%, 93.8%), and (92.4%, 94.7%) under C-Model II; and (93.0%, 93.5%), (91.6%, 93.8%), and (92.1%, 94.8%) under C-Model III. The CPs for the other parameters were similar and thus not reported here for brevity.

Table V presents the frequencies of ranking the true model as one of the top three models under each of the AIC, AICC, and BIC criteria. From Table V, we see that AIC outperforms both AICC and BIC when the full model is the correct model and the between-study variability is large. The results in this table also indicate that the performance of all three criteria improves when the between-study variability becomes smaller, and all three criteria perform well when the between-study variability is small. Under C-Model II, the percentages of ranking the true model as one of the top three models in the 1000 simulations were 85.2%, 93.9%, and 99.8% for AIC, 78.1%, 93.3%, and 99.8% for AICC, and 77.5%, 93.5%, and 99.8% for BIC when $V = V_0, V_0/2$, and $V_0/10$, respectively. In this sense, AIC performs slightly better than AICC and BIC. When C-Model III is the correct model, both AICC and BIC perform better than AIC. When the full model is the correct model, BIC performs slightly better than AICC, whereas AICC does slightly better than BIC when C-Models II and III are the correct models. Overall, AIC tends to select a larger model, whereas both AICC and BIC are in favor of smaller models.

In all nine simulation settings, we carried out the test of statistical homogeneity via the Q test statistic given by (3.4). The average values of Q_K were 1476.2, 761.0, and 188.3 for $V = V_0, V_0/2$, and $V_0/10$ under C-Model I; 1633.1, 840.0, and 204.9 for $V = V_0, V_0/2$, and $V_0/10$ under C-Model II; and 1778.2, 913.0, and 220.3 for $V = V_0, V_0/2$, and $V_0/10$ under C-Model III. In all nine simulations, the Q statistic rejected the hypothesis of homogeneity; that is, $V = 0$, 100% of the time in the 1000 simulated data sets, resulting in 100% power. We note

that $V_{01}/10 = \begin{pmatrix} 3.6 & -1.2 \\ -1.2 & 1.1 \end{pmatrix}$ and $V_{02}/10 = \begin{pmatrix} 1.8 & -1.6 \\ -1.6 & 2.2 \end{pmatrix}$, and, hence, the variances are relatively small compared with the effect sizes of the treatments. We also conducted a simulation study with $V = 0$. That is, we generated the data from (3.1) and (3.2) with $1_{jk} = 1_j$ and $2_{jk} = 2_j$ for $j = 1, 2$. Under C-Model I, the average value of Q_K was 44.7, and the Q test rejected the hypothesis that $V = 0$, 54 times in the 1000 simulations at a significance level of 0.05. Note that under this simulation setting, $\chi^2_{JK-2J-p} = \chi^2_{44}$, the 95th percentile of χ^2_{44} is 60.5, and hence, the average value of Q_K is much smaller than this chi-square percentile. This result implies that the type I error of the Q test was about 5%. For the 1000 data sets generated under C-Model I, we also fit all 15 reduced models with zero to three covariates and then performed the Q test for each of these models. In this case, all 15 regression models were misspecified. The average values of Q_k ranged from 198.3 to 635.2, the minimum values of Q_k ranged from 120.1 to 492.7, and all p -values were less than 0.00001 for these 15 models. Similar results were obtained under C-Models II and III. These results further demonstrate that the Q statistic can be used to test either heterogeneity or misspecification of the regression model as discussed in Section 3.2.

5. Analysis of low-density lipoprotein cholesterol data

For the LDL-C data, y_{jk} denotes the percent reduction of LDL-C and $w_{jk}^{-1} = SD_{jk}^2/n_{jk}$, where SD_{jk} and n_{jk} denote the standard deviation of the mean LDL-C and the sample size, respectively, for the j th treatment in the k th trial. There were $K = 26$ studies, the first-line and second-line therapies were ‘not on statin’ and ‘on statin’ prior to the trial, and there were two treatment arms ($J = 2$) corresponding to ‘statin alone’ and ‘statin + EZE’. We considered eight aggregate covariates, including baseline LDL-C, baseline HDL-C, and baseline TG, age in years, white (%), male (%), diabetes mellitus (DM) (%), and duration in weeks. Thus, we have $x_{jk} = ((\text{baseline LDL-C})_{jk}, (\text{baseline HDL-C})_{jk}, (\text{baseline TG})_{jk}, \text{age}_{jk}, \text{white}_{jk}, \text{male}_{jk}, \text{DM}_{jk}, \text{Duration}_{jk})$ and the vector of corresponding regression coefficients is $\beta = (\beta_1, \dots, \beta_8)$ with $p = 8$ under the full model. We carried out variable selection for the meta-analysis regression model given in (3.1). We computed AICs, AICCs, and BICs for all

$2^8 = 256$ possible models. Table VI shows the values of these measures for the top three AIC models along with the no covariate model. The top three AIC models were (baseline LDL-C, baseline HDL-C, Duration), (baseline LDL-C, Duration), and (baseline LDL-C, baseline HDL-C, age, Duration), and the corresponding AIC values were 315.7, 316.6, and 316.6. The top AIC model, (baseline LDL-C, baseline HDL-C, Duration), is the third best BIC model with $BIC=332.1$ and the sixth best AICC model with $AICC = 325.3$. The second best AIC model, (baseline LDL-C, Duration), is also the second best AICC and BIC model. The no covariate model and the full model had AIC values of 318.8 and 323.8, which were ranked 23 and 196, respectively. The no covariate model is the best AICC model as well as the best BIC model. The third best AICC model was the model with a single covariate, namely, Duration, which was the 13th best AIC model and the fourth best BIC model. The values of AICC, AIC, and BIC for the model (Duration) were 325.0, 318.5, and 332.3. As shown in the simulation study, AIC tends to select a larger model, whereas AICC and BIC are in favor of a smaller model as both AICC and BIC penalize the dimension of the model parameters more than AIC. In practice, AIC is more conservative and desirable compared with AICC and BIC in variable selection as it penalizes the dimension of the model parameters less and avoids the misidentification of potentially important covariates. Table VI also shows the values of Q_K . Thus, the Q_K test rejects the hypothesis of no heterogeneity, which implies that there was heterogeneity across the $K = 26$ studies. This was confirmed by the large values of the maximum likelihood estimates of the V_{jj} 's as shown in Table VII. In addition, we fit the meta-regression models with no random effects ($V = 0$), a single random effect for each of the first-line therapy trials ($V_{122} = 0$), a single random effect for each of the second-line therapy trials ($V_{222} = 0$), and a single random effect for all trials ($V_{122} = V_{222} = 0$). Under the best AIC model, the AIC values were 1632.9, 533.4, 395.3, and 643.5 corresponding to these four types of random effects models. These AIC values were much larger than 315.7 under the model with four random effects. Similar results were obtained under other covariate models. These results further confirmed that there was heterogeneity of treatment effects within first-line and within second-line trials.

Table VII shows the parameter estimates under the best AIC model. From this table, we see that baseline LDL-C and duration were significant with p -values of 0.0277 and 0.0181, respectively. The positive coefficient for baseline LDL-C in the model implies that the higher the baseline LDL-C value was, the lower the percent reduction in LDL-C. Similarly, the longer the study duration, the lower the percent reduction in LDL-C. This might be due to a full realization of the beneficial effect of statins over the first several weeks, which might be difficult to fully sustain over the long run because of a possible lack of drug compliance. The predicted percent changes from baseline in LDL-C for patients on statin and EZE/statin in first-line therapy studies were -38.50 and -50.47 , respectively. The predicted percent changes from baseline in LDL-C for patients on statin and EZE/statin in second-line therapy studies were -7.55 and -27.53 , respectively. The treatment differences for first-line and second-line therapy studies were -11.97 and -19.97 , respectively, which were statistically significant each with p -value < 0.0001 . The treatment difference for second-line therapy studies was significantly higher than that for first-line therapy studies. We also fitted two other models (no covariate model and a full model with all eight covariates) for sensitivity analysis. The results of these two models were consistent with the best AIC model as seen from Table VII.

Under the meta-analysis regression model specified by (3.1), (3.2), and (3.3), the three hypotheses stated in Section 2 can be mathematically written as $H_{01}: \mu_{12} = \mu_{11}$; $H_{02}: \mu_{22} = \mu_{21}$; and $H_{03}: \mu_{22} - \mu_{21} = \mu_{12} - \mu_{11}$. These three hypotheses were all rejected under the best AIC model as shown in Table VII. Rejection of these hypotheses implies that there were treatment differences within first-line and second-line studies, and there were unequal treatment differences between first-line and second-line studies. Rejection of these

hypotheses also indicates that EZE had a significant effect within first-line and second-line studies and that LDL-C lowering due to statin was different between first-line and second-line studies. It is worthwhile to note that the aggregate study-level estimates used in our meta-analysis were already adjusted for baseline LDL-C (along with other covariates which varied from study to study), and yet baseline LDL-C still remained a significant covariate in both the final AIC model and the full model. This indicates differences among study populations and study characteristics and again emphasizes the importance of incorporating study-level covariates into the meta-analysis model. It should also be noted that the no covariate model is nested in the best AIC model, whereas the best AIC model is nested in the full model. The nested nature of these three models allows us to make a formal statistical comparison of the three models via likelihood ratio tests. On the basis of the likelihood ratio tests, we found that the best AIC model provided a significantly better fit than the no covariate model (p -value = 0.0288); however, the full model did not provide a significantly better fit than the no covariate model because of possible over-fitting of the data (p -value = 0.2024); and, in addition, the best AIC model fit the data equally well as the full model (p -value = 0.8564). Interestingly, the maximum likelihood estimates of the treatment effects were similar in all three models.

The EM algorithm discussed in the Appendix was implemented using FORTRAN 95 with IMSL. The convergence criterion for the EM algorithm for obtaining the MLEs was that the squared distance of all the model parameters between the t th and $(t + 10)$ th iterations was less than 10^{-7} . This algorithm converged in approximately 1000 iterations for all models we considered in both the simulation study and the analysis of the LDL-C data. The FORTRAN 95 code is available upon request.

6. Discussion

Our goal in this investigation was to develop a novel class of models for meta-analysis incorporating study-level covariates and be able to fit these models in order to study the impact of study-level covariates on the response variable. We applied this technique to an important problem in the field of cholesterol reduction and studied the effect of adding EZE to a class of drugs called statins through aggregate meta-analysis controlling for some of the important study-level covariates. Our proposed variable selection procedure led us to our best AIC model with three covariates: baseline LDL-C, baseline HDL-C, and study duration. This model provided a significantly better fit over the model with no covariates. The model implied that the higher the baseline LDL-C is, the lower the percent reduction in LDL-C at study end. Also, the longer the study duration is, the lower the LDL-C percent reduction. The latter result is somewhat of a conjecture because the duration of the studies considered here (as well as for many other randomized clinical trials on statins) did not vary over a large range. The issue of the impact of study duration remains an open question needing further investigation. It is worthwhile to reiterate the importance of incorporating covariates in the meta-analysis model even though the aggregate study-level estimates used in the meta-analysis may have already adjusted for those covariates. Differences among study populations and study characteristics necessitates the inclusion of these covariates into the analysis.

The beneficial effects of statin therapy is well studied and well established. We studied the effect of combination therapy of EZE along with statins, and our meta-analysis has allowed us to clearly demonstrate enhanced reduction in LDL-C because of addition of EZE over and above that due to statins alone. This incremental reduction is clinically as well as statistically significant. Presently, Vytorin is the only drug approved in the USA by the FDA, which combines simvastatin and EZE into one tablet. Our analysis has also established larger between-treatment differences for second-line therapy compared with

first-line therapy. This implies a larger benefit for combination therapy over statins alone for patients already on statins (second-line therapy patients).

In summary, our analysis results with this rich dataset reveal the following: (i) statin therapy is effective, but statins in combination with EZE are even more effective in reducing LDL-C; (ii) the treatment difference (for % change from baseline) was higher in the second-line studies and can be attributed, in part, to lower baseline LDL-C values; (iii) baseline LDL-C, baseline HDL-C, and study duration are important covariates in LDL-C reduction; (iv) while conducting an aggregate meta-analysis, it is critical to incorporate study-level covariates, which is not a common practice, and the number of covariates that can be included in the model is dependent upon the number of studies included in the meta-analysis; and (v) even though the study-level estimates used in the meta-analysis may be adjusted locally (within study) for some of the covariates, it is still critical to incorporate these covariates in the meta-analysis model; in other words, adjusting for covariates at the study level is not sufficient.

As the model fitting is now done at the study level, one must be careful not to fit too large of a meta-regression model relative to the number of studies, and the results should be interpreted with caution. In our case study, we had 26 studies, and each study had two treatment arms, which yielded 52 data points. The largest model we fit contained 18 parameters, and so we had 34 degrees of freedom left over. In the meta-analysis literature, there are no current guidelines discussing how large of a model to fit relative to the number of studies. One needs to use common sense and practical judgment and fit models that yield stable estimates and SEs, especially for the variance components. In our case study, the estimates from the largest model were quite stable, and the EM algorithm always converged in relatively few iterations, thus giving us confidence that the models we fit were reasonable. On the basis of our experience with these data, we would recommend a general rule of thumb for model fitting that $n \geq 2q$, where n denotes the number of data points and q denotes the total number of parameters in the meta-regression model. In carrying out a variable selection procedure, there may be an inherent multiplicity issue in the covariate selection procedure, and as a result one must bear this in mind when carrying out such a procedure and perhaps conduct simulation studies to examine whether the type I error is controlled with a given procedure. At the very least, this issue must be acknowledged by the data analyst.

In Section 3.1, we assume that w_{jk} is a known precision. Because we have only a single observation for the j th treatment within the k th trial, w_{jk} is not estimable. We need additional information to estimate w_{jk} . Suppose that the standard deviation, SD_{jk} , is available. Then, the method recently proposed by Yao *et al.* [30] can be used to relax the assumption that w_{jk} is known. Specifically, (3.2) needs to be replaced by two equations:

$$\varepsilon_{jk} \sim N \left(0, \frac{\sigma_{jk}^2}{n_{jk}} \right) \quad (3.2a)$$

and

$$\frac{(n_{jk}-1)SD_{jk}^2}{\sigma_{jk}^2} \sim \chi_{n_{jk}-1}^2, \quad (3.2b)$$

where σ_{jk}^2 is an unknown variance. As shown in [30], using the profile likelihood approach, the model using (3.1), (3.2a), and (3.2b) reduces to the model (3.1) when w_{jk} follows a scaled

Student- t distribution with $n_{jk} - 1$ degrees of freedom and scale parameter $w_{jk}^{-1} = \frac{SD_{jk}^2}{n_{jk}}$ after profiling out σ_{jk}^2 . When n_{jk} is large, the Student- t distribution is approximately normal.

Thus, the model using (3.1) and (3.2) with a fixed variance $w_{jk}^{-1} = \frac{SD_{jk}^2}{n_{jk}}$ is approximately the same as the model defined by (3.1), (3.2a), and (3.2b) when n_{jk} is relatively large. For the LDL-C data, the smallest sample size was 92. Thus, we do not need to estimate w_{jk} , and

instead, we can simply set $w_{jk}^{-1} = \frac{SD_{jk}^2}{n_{jk}}$.

We mention here that the proposed methodology is quite general and can be applied in any meta-analysis setting including a wide range of scientific applications. We have focused here specifically on cholesterol-lowering drugs because of our collaborations in this area and the availability of several datasets. Future work includes extending the proposed methodology to multivariate responses in meta-analysis models, such as joint modeling of the percent reduction of LDL-C from baseline, the percent change of HDL-C from baseline, and the percent reduction of TG from baseline, on the basis of individual patient data or study-level data. Covariate data are commonly missing at the study level in meta-analysis, such as body mass index. The literature for analyzing such missing data is quite sparse. Currently, these clinically important extensions are under investigation.

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Appendix: The complete-data likelihood function and expectation–maximization algorithm for meta-regression models

The complete-data likelihood function

Let $\xi = (\xi'_1, \xi'_2, \dots, \xi'_K)'$ be the vector of unknown latent variables as defined in (3.3). Then, the conditional distribution of $\mathbf{y}_k$ given ϕ and ξ_k is of the form

$$\begin{aligned} f(\mathbf{y}_k | X_k, Z_k, \phi, \xi_k) &= \prod_{j=1}^J \left(\frac{w_{jk}}{2\pi} \right)^{1/2} \exp \left\{ -\frac{w_{jk}}{2} (y_{jk} - \tilde{x}'_{jk}\phi - z'_{jk}\xi_k)^2 \right\} \\ &= \left\{ \prod_{j=1}^J \left(\frac{w_{jk}}{2\pi} \right)^{1/2} \right\} \exp \left\{ -\frac{1}{2} (\mathbf{y}_k - X_k\phi - Z_k\xi_k)' W_k (\mathbf{y}_k - X_k\phi - Z_k\xi_k) \right\}, \end{aligned}$$

where $X_k = (\mathbf{x}_{1k}, \mathbf{x}_{2k})$, and conditional on V , ξ_k has the density

$f(\xi_k | V) = \frac{|V|^{-1/2}}{(2\pi)^J} \exp(-\frac{1}{2}\xi'_k V^{-1}\xi_k)$. Ignoring the constants that are free of ξ_k and $\exp$, the complete-data log-likelihood is given by

$$\ell(\eta, \xi) = \sum_{k=1}^K \ell(\eta; \mathbf{y}_k, \xi_k) = \sum_{k=1}^K \left[\left\{ -\frac{1}{2} (\mathbf{y}_k - X_k\phi - Z_k\xi_k)' W_k (\mathbf{y}_k - X_k\phi - Z_k\xi_k) \right\} + \left(-\frac{1}{2} \log|V| - \frac{1}{2} \xi'_k V^{-1} \xi_k \right) \right]. \quad (\text{A.1})$$

Expectation–maximization algorithm for meta-regression models

We develop an efficient EM algorithm to compute the maximum likelihood estimates of η via the EM by the method of Weights, which was initially introduced by Ibrahim [31] and further developed by Ibrahim, Chen, and Lipsitz [32] in the context of generalized linear models with non-ignorable missing covariate data. The algorithm involves two steps: the E-step and the M-step. Let $\eta^{(t)} = (\phi^{(t)}, (V^{-1})^{(t)})$ denote the value of η at the t th EM iteration. Note that at the initial EM iteration, $V^{(0)}$ must be chosen to be a block diagonal matrix with a structure similar to V . To compute the E-step, we must compute the expectation of the complete-data log-likelihood (A.1) with respect to the conditional distribution of the latent variables ξ_k given the observed data. We can write the E-step for the observations from the k th trial at the $(t+1)$ st EM iteration as

$$\begin{aligned} Q_k(\eta | \eta^{(t)}) &= \int \ell(\eta; \mathbf{y}_k, \xi_k) f(\xi_k | \mathbf{y}_k, \eta^{(t)}) d\xi_k \\ &= \int \left\{ -\frac{1}{2} (\mathbf{y}_k - X_k\phi - Z_k\xi_k)' W_k (\mathbf{y}_k - X_k\phi - Z_k\xi_k) \right\} f(\xi_k | \mathbf{y}_k, \eta^{(t)}) d\xi_k + \\ &\quad \int \left(-\frac{1}{2} \log|V| - \frac{1}{2} \xi'_k V^{-1} \xi_k \right) f(\xi_k | \mathbf{y}_k, \eta^{(t)}) d\xi_k, \end{aligned}$$

where $f_k(\mathbf{y}_k | \boldsymbol{\eta}^{(t)})$ is the conditional distribution of $\mathbf{y}_k$ given the observed data $\mathbf{y}_k$ and the value of $\boldsymbol{\eta}$ at the t th EM iteration. After much tedious algebra, it can be shown that $f_k(\mathbf{y}_k | \boldsymbol{\eta}^{(t)}) \sim N(\boldsymbol{\xi}_k^{(t)}, \sum_k^{(t)})$, where $\boldsymbol{\xi}_k^{(t)} = \sum_k^{(t)} Z_k' W_k (\mathbf{y}_k - X_k \boldsymbol{\phi}^{(t)})$ and $\sum_k^{(t)} = \{Z_k' W_k Z_k + (V^{(t)})^{-1}\}^{-1}$. After some algebra, $Q_k(\boldsymbol{\eta} | \boldsymbol{\eta}^{(t)})$ reduces to

$$\begin{aligned} Q_k(\boldsymbol{\eta} | \boldsymbol{\eta}^{(t)}) &= -\frac{1}{2} \left\{ (\mathbf{y}_k - X_k \boldsymbol{\phi} - Z_k \boldsymbol{\xi}_k^{(t)})' W_k (\mathbf{y}_k - X_k \boldsymbol{\phi} - Z_k \boldsymbol{\xi}_k^{(t)}) + \text{tr} \left(Z_k' W_k Z_k \sum_k^{(t)} \right) \right\} \\ &\quad - \frac{1}{2} \log |V| \\ &\quad - \frac{1}{2} \boldsymbol{\xi}_k^{(t)'} V^{-1} \boldsymbol{\xi}_k^{(t)} \\ &\quad - \frac{1}{2} \text{tr} \left(V^{-1} \sum_k^{(t)} \right). \end{aligned}$$

Thus, the E-step for all the observations from the K trials is given by

$$Q(\boldsymbol{\eta} | \boldsymbol{\eta}^{(t)}) = \sum_{k=1}^K Q_k(\boldsymbol{\eta} | \boldsymbol{\eta}^{(t)}).$$

The M-step maximizes $Q(\boldsymbol{\eta} | \boldsymbol{\eta}^{(t)})$, and closed forms for the parameter estimates are available. Specifically, the M-step is obtained as follows. First, we find $V^{(t+1)}$ to maximize

$$Q_V = -\frac{K}{2} \log |V| - \frac{1}{2} \sum_{k=1}^K \boldsymbol{\xi}_k^{(t)'} V^{-1} \boldsymbol{\xi}_k^{(t)} - \frac{1}{2} \sum_{k=1}^K \text{tr} \left(V^{-1} \sum_k^{(t)} \right),$$

which gives

$$V^{(t+1)} = \frac{1}{K} \sum_{k=1}^K \left\{ \boldsymbol{\xi}_k^{(t)} \boldsymbol{\xi}_k^{(t)'} + \sum_k^{(t)} \right\}.$$

Second, we find $\boldsymbol{\phi}^{(t+1)}$ to minimize $Q_\phi = \sum_{k=1}^K (\mathbf{y}_k - X_k \boldsymbol{\phi} - Z_k \boldsymbol{\xi}_k^{(t)})' W_k (\mathbf{y}_k - X_k \boldsymbol{\phi} - Z_k \boldsymbol{\xi}_k^{(t)})$, which yields

$$\boldsymbol{\phi}^{(t+1)} = \left(\sum_{k=1}^K X_k' W_k X_k \right)^{-1} \sum_{k=1}^K X_k' W_k (\mathbf{y}_k - Z_k \boldsymbol{\xi}_k^{(t)}).$$

Let $\hat{\boldsymbol{\eta}}$ denote the estimate of $\boldsymbol{\eta}$ at EM convergence. To obtain the asymptotic covariance matrix of $\hat{\boldsymbol{\eta}}$, we use the method of Louis [33]. Following a similar derivation as in [34], the estimated observed information matrix of $\hat{\boldsymbol{\eta}}$ is given by

$$\mathcal{J}(\hat{\eta}) = -\ddot{Q}(\hat{\eta}|\hat{\eta}) - \left\{ \sum_{k=1}^K E \left[S_k(\hat{\eta}; \mathbf{y}_k, \boldsymbol{\xi}_k) S_k(\hat{\eta}; \mathbf{y}_k, \boldsymbol{\xi}_k)' | \mathbf{y}_k, \hat{\eta} \right] = \sum_{k=1}^N \dot{Q}_k(\hat{\eta}|\hat{\eta}) \dot{Q}_k(\hat{\eta}|\hat{\eta})' \right\}, \quad (\text{A.2})$$

where $\hat{\eta}$ is the estimate of η at convergence,

$$S_k(\hat{\eta}; \mathbf{y}_k, \boldsymbol{\xi}_k) = \left[\frac{\partial \ell(\eta; \mathbf{y}_k, \boldsymbol{\xi}_k)}{\partial \eta} \right]_{\eta=\hat{\eta}},$$

$\dot{Q}$ denotes the first derivative vector of Q with respect to η , and $\ddot{Q}$ denotes the second derivative matrix of Q with respect to η . The expectation in (A.2) is taken with respect to the density $f(\mathbf{y}_k | \eta)$.

The estimate of the asymptotic covariance matrix of $\hat{\boldsymbol{\phi}}$ is the upper $p^* \times p^*$ block of $[\mathcal{I}(\hat{\boldsymbol{\phi}})]^{-1}$, where $p^* = p + 2J$ is the dimension of $\boldsymbol{\phi}$. Straightforward derivations yield

$$\frac{\partial Q_k(\eta | \eta^{(t)})}{\partial \boldsymbol{\phi}} = X_k' W_k (\mathbf{y}_k - Z_k \boldsymbol{\xi}_k^{(t)}) - (X_k' W_k X_k) \boldsymbol{\phi} \text{ and } \frac{\partial^2 Q_k(\eta | \eta^{(t)})}{\partial \boldsymbol{\phi} \partial \boldsymbol{\phi}'} = -X_k' W_k X_k. \quad (\text{A.3})$$

Write $V^* = V^{-1}$, $V^* = \text{diag}(V_1^*, V_2^*)$, where $V_\ell^* = V_\ell^{-1} = (V_{\ell jj'}^*)_{j \times j'}$ for $\ell = 1, 2$. Let

$$v(V_\ell^*) = (V_{\ell 11}^*, V_{\ell 21}^*, \dots, V_{\ell J1}^*, V_{\ell 22}^*, \dots, V_{\ell J2}^*, \dots, V_{\ell JJ}^*)',$$

which is formed by stacking the columns of the lower triangular portion of V_ℓ^* and

$$\text{vec}(V_\ell^*) = (V_{\ell 11}^*, \dots, V_{\ell J1}^*, \dots, V_{\ell 12}^*, \dots, V_{\ell J2}^*, \dots, V_{\ell 1J}^*, \dots, V_{\ell JJ}^*)',$$

which is formed by stacking the columns of V_ℓ^* . Then, we have

$$\frac{\partial^2 Q_k(\eta | \eta^{(t)})}{\partial \gamma \partial v(V_\ell^*)'} = \mathbf{0}$$

for $\ell = 1, 2$. Notice that $\boldsymbol{\xi}_k(t)$ is a block diagonal matrix. Then, we can write

$$\begin{aligned} Q_{k, V^*}(\eta | \eta^{(t)}) &= \frac{1}{2} \log |V^*| - \frac{1}{2} \boldsymbol{\xi}_k^{(t)'} V^* \boldsymbol{\xi}_k^{(t)} - \frac{1}{2} \text{tr}(V^* \sum_k^{(t)}) \\ &= \frac{1}{2} \log |V_1^*| - \frac{1}{2} \boldsymbol{\xi}_{1k}^{(t)'} V_1^* \boldsymbol{\xi}_{1k}^{(t)} - \frac{1}{2} \text{tr} \left(V_1^* \sum_{1k}^{(t)} \right) \\ &\quad + \frac{1}{2} \log |V_2^*| - \frac{1}{2} \boldsymbol{\xi}_{2k}^{(t)'} V_2^* \boldsymbol{\xi}_{2k}^{(t)} - \frac{1}{2} \text{tr} \left(V_2^* \sum_{2k}^{(t)} \right), \end{aligned} \quad (\text{A.4})$$

where $\xi_k^{(t)} = (\xi_{1k}^{(t)'}, \xi_{2k}^{(t)'})'$, $\sum_k^{(t)} = \text{diag}(\sum_{1k}^{(t)}, \sum_{2k}^{(t)})$, and $\xi_{\ell k}^{(t)'} is a J -dimensional vector, and $\sum_{\ell k}^{(t)}$ is a $J \times J$ symmetric matrix for $\ell = 1, 2$. Using the matrix derivative formula given in [35], we obtain$

$$\frac{\partial Q_k(\eta|\eta^{(t)})}{\partial v(V_\ell^*)} = \frac{1}{2} D_J' \left\{ \text{vec}(V_\ell^{*-1}) - \text{vec} \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} + \sum_{\ell k}^{(t)} \right) \right\}, \quad (\text{A.5})$$

where D_J is the $J^2 \times J(J+1)/2$ duplicated matrix such that $D_J v(V_\ell^*) = \text{vec}(V_\ell^*)$. When $J=2$,

$$D_2 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

Again, using the matrix derivative formula given in [35], we have

$$\frac{\partial^2 Q_k(\eta|\eta^{(t)})}{\partial v(V_\ell^*) \partial v(V_\ell^*)'} = -\frac{1}{2} D_J' \left(V_\ell^{*-1} \otimes V_\ell^{*-1} \right) D_J, \quad (\text{A.6})$$

where $\otimes$ denotes the Kronecker product, for $\ell = 1, 2$. Furthermore, we have $\frac{\partial^2 Q_k(\eta|\eta^{(t)})}{\partial v(V_1^*) \partial v(V_2^*)'} = \mathbf{0}$. Using (A.3), (A.5), and (A.6) with both $\eta^{(t)}$ and η replaced by $\eta^{(t)}$, we can easily obtain closed-form expressions of $Q(\eta^{(t)})$ and $Q_k(\eta^{(t)})$.

Using the complete-data log-likelihood $\ell(\eta, \mathbf{y}_k)$, we have

$$\begin{aligned} \ell(\eta; \mathbf{y}_k, \xi_k) &= -\frac{1}{2} (\mathbf{y}_k - X_k \phi - Z_k \xi_k)' W_k (\mathbf{y}_k - X_k \phi - Z_k \xi_k) + \frac{1}{2} \log |V_1^*| \\ &\quad - \frac{1}{2} \xi_{1k}' V_1^* \xi_{1k} + \frac{1}{2} \log |V_2^*| - \frac{1}{2} \xi_{2k}' V_2^* \xi_{2k}, \end{aligned}$$

where $\xi_k = (\xi_{1k}, \dots, \xi_{Jk})'$ for $\ell = 1, 2$. Similar to (A.3) and (A.5), we obtain

$$S_{k,1} = \frac{\partial \ell(\eta; \mathbf{y}_k, \xi_k)}{\partial \phi} = X_k' W_k (\mathbf{y}_k - Z_k \xi_k) - (X_k' W_k X_k) \phi$$

and

$$S_{k,1+\ell} = \frac{\partial \ell(\eta; \mathbf{y}_k, \xi_k)}{\partial v(V_\ell^*)} = \frac{1}{2} D_J' \left\{ \text{vec}(V_\ell^{*-1}) - \text{vec}(\xi_{\ell k} \xi_{\ell k}') \right\}$$

for $k = 1, 2$. Write $Z_k = (Z_{1k}, Z_{2k})$, where $Z_{1k} = ((1 - I_k)e_1, \dots, (1 - I_k)e_J)$ and $Z_{2k} = (I_k e_1, \dots, I_k e_J)$. After some tedious algebra, we obtain

$$E \left[S_{k,1} S'_{k,1} | \mathbf{y}_k, \hat{\eta}^{(t)} \right] = X'_k W_k \left\{ \left(\mathbf{y}_k - X_k \phi - Z_k \hat{\xi}_k^{(t)} \right) \left(\mathbf{y}_k - X_k \phi - Z_k \hat{\xi}_k^{(t)} \right)' + Z_k \sum_k^{(t)} Z_k' \right\} W_k X_k \quad (\text{A.7})$$

and

$$E \left[S_{k,1} S'_{k,1+\ell} | \mathbf{y}_k, \hat{\eta}^{(t)} \right] = \frac{1}{2} \left\{ X'_k W_k \left(\mathbf{y}_k - X_k \phi - Z_k \hat{\xi}_k^{(t)} \right) \text{vec} \left(V_\ell^{*-1} - \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} + \sum_{\ell k}^{(t)} \right) \right)' \right. \\ \left. + X'_k W_k Z_{\ell k} \left(\xi_{\ell k}^{(t)'} \otimes \sum_{\ell k}^{(t)} + \sum_{\ell k}^{(t)} \otimes \xi_{\ell k}^{(t)'} \right) \right\} D_J \quad (\text{A.8})$$

for $k = 1, 2$. Now, we let K_{JJ} denote a $J^2 \times J^2$ commutation matrix such that $\text{vec}(A) = K_{JJ} \text{vec}(A')$, where A is a $J \times J$ matrix. Also let $N_J = \frac{1}{2}(I_{J^2} + K_{JJ})$, where I_{J^2} is the $J^2 \times J^2$ identity matrix. Note that

$$\begin{aligned} \text{vec}(\xi_{\ell k} \xi_{\ell k}') &= \text{vec} \left(\left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right)' \right) + \text{vec} \left(\left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) \hat{\xi}_{\ell k}^{(t)'} \right) \\ &\quad + \text{vec} \left(\hat{\xi}_{\ell k}^{(t)} \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right)' \right) + \text{vec} \left(\hat{\xi}_{\ell k}^{(t)} \hat{\xi}_{\ell k}^{(t)'} \right) \\ &= \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) \otimes \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) + \hat{\xi}_{\ell k}^{(t)} \otimes \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) + \left(\xi_{\ell k} - \hat{\xi}_{\ell k}^{(t)} \right) \otimes \hat{\xi}_{\ell k}^{(t)} + \hat{\xi}_{\ell k}^{(t)} \otimes \hat{\xi}_{\ell k}^{(t)} \end{aligned}$$

for $k = 1, 2$. Using Theorem 9.20 of [35] and after some algebra, we obtain

$$E \left[S_{k,1+\ell} S'_{k,1+\ell} | \mathbf{y}_k, \hat{\eta}^{(t)} \right] = \frac{1}{4} D_J' \left[\text{vec} \left(V_\ell^{*-1} - \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} + \sum_{\ell k}^{(t)} \right) \right) \text{vec} \left(V_\ell^{*-1} - \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} + \sum_{\ell k}^{(t)} \right) \right)' \right. \\ \left. + 2N_J \left\{ \sum_{\ell k}^{(t)} \otimes \sum_{\ell k}^{(t)} + \sum_{\ell k}^{(t)} \otimes \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} \right) + \left(\xi_{\ell k}^{(t)} \xi_{\ell k}^{(t)'} \right) \otimes \sum_{\ell k}^{(t)} \right\} \right] D_J \quad (\text{A.9})$$

for $k = 1, 2$. Finally, we obtain

$$E \left[S_{k,2} S'_{k,3} | \mathbf{y}_k, \hat{\eta}^{(t)} \right] = \frac{1}{4} D_J' \text{vec} \left(V_1^{*-1} - \left(\xi_{1k}^{(t)} \xi_{1k}^{(t)'} + \sum_{1k}^{(t)} \right) \right) \text{vec} \left(V_2^{*-1} - \left(\xi_{2k}^{(t)} \xi_{2k}^{(t)'} + \sum_{2k}^{(t)} \right) \right)' D_J. \quad (\text{A.10})$$

We therefore obtain a closed-form expression of $E[S_k(\cdot; \mathbf{y}_k, \cdot) S_k'(\cdot; \mathbf{y}_k, \cdot) | \mathbf{y}_k, \cdot]$ in (A.2) via (A.7)–(A.10) with $\hat{\eta}^{(t)}$ and $\cdot$ replaced by $\cdot$.

Figure 1.

Forest plots of LDL-C data, where each line corresponds to percent reduction in LDL-C from baseline with a 95% confidence interval.

Table I

Information on the first-line studies to be included in meta-analysis I.

Study	Title	Treatment groups	Treatment duration (weeks)	Primary manuscript reference
1	A multicenter, double-blind, randomized, placebo-controlled, 'factorial' design, 12-week study to evaluate the efficacy of ezetimibe 10 mg/day co-administered with multiple doses of simvastatin in patients with primary hypercholesterolemia	Placebo; EZE 10 mg; SIMVA 10, 20, 40, 80 mg; EZE 10 mg + SIMVA 10, 20, 40, 80 mg	12	Goldberg A <i>et al.</i> , <i>Mayo Clin Proc</i> 2004; 79:620–629
2	A phase III double-blind efficacy and safety study of ezetimibe (SCH 58235) 10 mg in addition to pravastatin compared with placebo in subjects with primary hypercholesterolemia (Protocol P00691)	Placebo; EZE 10 mg; PRAVA 10, 20, 40 mg; EZE 10 mg + PRAVA 10, 20, 40 mg	12	Melani L <i>et al.</i> , <i>European Heart J</i> 2003; 24:717–728
3	Schering Plough clinical study report, multicenter study: a phase III double-blind efficacy and safety study of ezetimibe 10 mg in addition to simvastatin compared with placebo in subjects with primary hypercholesterolemia	Placebo; EZE 10 mg; SIMVA 10, 20, 40, 80 mg; EZE 10 mg + SIMVA 10, 20, 40, 80 mg	12	Davidson M <i>et al.</i> , <i>J Am Coll Cardiol</i> 2002; 40:2125–2134
4	A comparison of treatment with ezetimibe and simvastatin coadministration versus simvastatin in attaining the NCEP ATP III CHD or CHD-risk equivalent strata LDL-C target level	EZE/SIMVA 10/10 mg; EZE/SIMVA 10/20 mg; EZE/SIMVA 10/40 mg; SIMVA 20 mg	23 Titration (only use week 5)	Feldman T <i>et al.</i> , <i>Am J Cardiol</i> 2004 Jun 15; 93(12): 1481–1486
5	Randomized, double-blind, parallel group, 28-week study to evaluate the efficacy and safety of ezetimibe and simvastatin coadministration versus atorvastatin in patients with hypercholesterolemia	EZE/SIMVA 10/10 mg; EZE/SIMVA 10/20 mg; ATORVA 10 mg	24 Titration (only use week 6)	Ballantyne CM <i>et al.</i> , <i>Am J Cardiol</i> 2004 Jun 15; 93(12): 1487–1494
6	A multicenter, randomized, double-blind, placebo-controlled, 'factorial' design study to evaluate the lipid-altering efficacy and safety of ezetimibe/simvastatin combination tablet in patients with primary hypercholesterolemia extension: a multicenter, randomized, double-blind, 'factorial' design, 14-week extension study to evaluate the lipid-altering efficacy and safety of ezetimibe/simvastatin combination tablet in patients with primary hypercholesterolemia	Placebo; EZE 10 mg; SIMVA 10, 20, 40, 80 mg; EZE 10 mg + SIMVA 10, 20, 40, 80 mg	12	Bays HE <i>et al.</i> , <i>Clin Ther</i> 2004; 26(11):1758–1773
7	A multicenter, double-blind, randomized, parallel group, 6-week study to evaluate the efficacy and safety of ezetimibe/simvastatin combination tablet versus atorvastatin in patients with hypercholesterolemia	EZE/SIMVA 10/10, 10/20, 10/40, 10/80 mg; ATORVA 10, 20, 40, 80 mg	6	Ballantyne CM <i>et al.</i> , <i>Am Heart J</i> 2005; 149(3):464–473
8	A multicenter, randomized, double-blind study to evaluate the lipid-altering efficacy and safety of the ezetimibe/simvastatin combination tablet versus rosuvastatin in patients with primary hypercholesterolemia	EZE/SIMVA 10/20, 10/40, 10/80 mg; ROSUVA 10, 20, 40 mg	6	Catapano AL <i>et al.</i> , <i>CMRO</i> 2006; 22(10): 2041–2053
9	A multicenter, double-blind, randomized, parallel group, 6-week study to evaluate the efficacy and safety of ezetimibe/simvastatin combination tablet versus atorvastatin in patients with type 2 diabetes mellitus (T2DM) and hypercholesterolemia	EZE/SIMVA 10/20, 10/40 mg; ATORVA 10, 20, 40 mg	6	Ronald B <i>et al.</i> , <i>Mayo Clin Proc</i> 2006; 81:1579–1588
10	A phase III double-blind efficacy and safety study of ezetimibe (SCH 58235) 10 mg in addition to lovastatin compared with placebo in subjects with primary hypercholesterolemia (Protocol P00679)	Placebo; EZE 10 mg; LOVA 10, 20, 40 mg; EZE 10 mg + LOVA 10, 20, 40 mg	12	Kerzner B <i>et al.</i> , <i>Am J Cardiol</i> 2003; 91(4): 418–424

Study	Title	Treatment groups	Treatment duration (weeks)	Primary manuscript reference
11	A phase III, double-blind efficacy and safety study of ezetimibe (SCH 58235) 10 mg in addition to atorvastatin compared with placebo in subjects with primary hypercholesterolemia (Protocol P00692)	Placebo; EZE 10 mg; ATORVA 10, 20, 40, 80 EZE 10 mg + ATORVA 10, 20, 40, 80 mg	12	Ballantyne CM <i>et al.</i> , <i>Circulation</i> 2003; 107:2409–2415
12	A multicenter, randomized, double-blind study to evaluate the efficacy and safety of ezetimibe/simvastatin versus atorvastatin in high CHD-risk patients with metabolic syndrome and hypercholesterolemia	EZE/SIMVA 10/20, 10/40 mg; ATORVA 10, 20, 40 mg	6	Robinson <i>et al.</i> , <i>Am J Cardiol</i> 2009; 103(12): 1694–1702
13	A multicenter, double-blind, randomized study to evaluate the lipid-altering efficacy, safety, and tolerability of ezetimibe co-administered with simvastatin versus simvastatin monotherapy in African American subjects with primary hypercholesterolemia	SIMVA 20 mg; EZE 10 + SIMVA 20 mg	12	Rodney R <i>et al.</i> , <i>J Natl Med Assoc</i> 2006; 98:772–778

EZE, ezetimibe; SIMVA, simvastatin; PRAVA, pravastatin; ATORVA, atorvastatin; ROSUVA, rosuvastatin. NCEP, National Cholesterol Education Program; ATP, Adult Treatment Panel; CHD, coronary heart disease.

Table II

Information on the second-line studies to be included in meta-analysis II.

Study	Title	Treatment groups	Treatment duration (weeks)	Primary manuscript reference
14	A multicenter, double-blind, randomized, placebo-controlled, parallel group, 6-week study to evaluate the efficacy and safety of ezetimibe 10 mg/day when added to ongoing therapy with a statin versus statin therapy alone, in patients with hypercholesterolemia	Ongoing statin +, placebo, EZE 10 mg	6	Pearson et al., <i>Mayo Clin Proc</i> 2005; 80(5): 587–595
15	A randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of EZE co-administered with atorvastatin in hypercholesterolemic patients with CHD who had not reached LDL goal < 100 mg/dl on atorvastatin alone	Ongoing ATORVA + placebo, EZE 10 mg	6	Cruz-Fernandez JM et al., <i>Int J Clin Pract</i> 2005; 59(6):619–627
16	A double-blind efficacy and safety study of ezetimibe 10 mg in addition to atorvastatin in subjects with coronary heart disease or multiple cardiovascular risk factors and with primary hypercholesterolemia not controlled by a starting dose (10 mg) of atorvastatin (p00693)	Ongoing ATORVA 10 => EZE/ATORVA 10/10 mg; ATORVA 20 mg	14 Titration (only use week 4)	Stein E et al., <i>Am Heart J</i> 2004 Sep; 148(3): 447–455
17	Randomized, double-blind, parallel, multicenter study to evaluate the efficacy and safety of simvastatin monotherapy compared with simvastatin plus ezetimibe (SCH 58235) in type 2 diabetic patients treated with thiazolidinediones	Ongoing SIMVA => EZE/SIMVA 10/20 mg; SIMVA 40 mg	14 (the end point was an average of week 6, 12, and 24)	Gaudiani LM et al., <i>Diabetes Obes Metab</i> 2005 Jan; 7(1):88–97
18	A multicenter, randomized, double-blind, titration study to evaluate and compare the efficacy and safety of ezetimibe added on to atorvastatin 20 mg versus up titration to atorvastatin 40 mg in hypercholesterolemic patients at moderately high risk for coronary heart disease not adequately controlled on atorvastatin 20 mg	Ongoing ATORVA 20 => EZE/ATORVA 10/20 mg; ATORVA 40 mg	6	Conard SE et al., <i>Am J Cardiol</i> 2008; 102(11):1489–1494
19	A multicenter, randomized, double-blind, titration study to evaluate and compare the efficacy and safety of ezetimibe added on to atorvastatin 40 mg versus up titration to atorvastatin 80 mg in hypercholesterolemic patients at high risk for coronary heart disease not adequately controlled on atorvastatin 40 mg	Ongoing ATORVA 40 => EZE/ATORVA 10/40 mg; ATORVA 80 mg	6	Leiter LA et al., <i>Am J Cardiol</i> 2008; 102(11):1495–1501
20	Randomized, double-blind, placebo-controlled study to evaluate efficacy, safety, and tolerability of ezetimibe 10 mg or placebo co-administered with existing simvastatin 10 or 20 mg in attaining low-density lipoprotein cholesterol target levels in patients with hypercholesterolemia and coronary heart disease	Ongoing SIMVA + Placebo; EZE 10 mg	6	Brohet C et al., <i>CMRO</i> 2005; 21(4):571–578
21	A multicenter, randomized, double-blind, parallel arm, 12-week study to evaluate the efficacy and safety of ezetimibe 10 mg when added to atorvastatin 10 mg versus titration to atorvastatin 20 mg and to 40 mg in elderly patients with hypercholesterolemia at high risk for CHD	Ongoing ATORVA 10 => EZE/ATORVA 10/10 mg; ATORVA 20 mg	12 Titration (only use week 6)	Zieve F et al., <i>Am J Cardiol</i> 2010; 105(5): 656–663
22	A randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy, safety, and tolerability of ezetimibe 10 mg or placebo co-administered with existing simvastatin 10 or 20 mg in attaining low-density lipoprotein cholesterol target levels in patients with hypercholesterolemia and coronary heart disease	Ongoing SIMVA + Placebo; EZE 10 mg	6	Farnier J et al., <i>Int J Cardiol</i> 2005; 102:327–332
23	A randomized, double-blind, active-controlled study to assess the LDL-C lowering of switching to a combination tablet EZE/simvastatin (10 mg/20 mg) compared with doubling the dose of atorvastatin from 10 to 20	Ongoing ATORVA 10 => EZE/SIMVA 10/20 mg; ATORVA 20 mg	6	Barrios V et al., <i>Int J Clin Pract</i> 2005 Dec; 59(12):1377–1386

Study	Title	Treatment groups	Treatment duration (weeks)	Primary manuscript reference
24	mg in patients with hypercholesterolemia and atherosclerotic or coronary vascular disease A double-blind, multicenter study to assess the LDL-C lowering of combination tablets ezetimibe/simvastatin (10 mg/20 mg) and ezetimibe/simvastatin (10 mg/40 mg) compared with atorvastatin 20 mg in patients with type II diabetes	Ongoing ATORVA 10 => EZE/SIMVA 10/20 mg EZE/SIMVA 10/40 mg; ATORVA 20 mg	6	C. Constance <i>et al.</i> , <i>Diabetes Obes Metab</i> , 2007, 9(4):575-84
25	A randomized, double-blind, active-controlled study to assess the LDL-C lowering of switching to a combination tablet ezetimibe/simvastatin (10 mg/20 mg) compared with rosuvastatin 10 mg in patients with primary hypercholesterolemia and high cardiovascular risk and not adequately controlled with a prior statin	Ongoing statin => EZE/SIMVA 10/20 mg; ROSUVA 10 mg	6	Farmier M <i>et al.</i> , <i>IJCP</i> , 2009; 63:547-559
26	A multicenter, double-blind, randomized, placebo-controlled study to evaluate the lipid-altering efficacy, safety, and tolerability of SCH 58235 when added to ongoing therapy with an HMG-CoA reductase inhibitor (statin) in patients with primary hypercholesterolemia, known coronary heart disease, or multiple cardiovascular risk factors (P02173, P02246).	Ongoing statin + Placebo; EZE 10 mg	8	Gagne C <i>et al.</i> , <i>Am J Cardiol</i> 2002; 90:1084-1091

EZE, ezetimibe; SIMVA, simvastatin; ATORVA, atorvastatin; ROSUVA, rosuvastatin. CHD, coronary heart disease.

Table III

Patient entry criteria of the studies to be included in meta-analysis.

Study	Age (years)	LDL-C	Entry criteria					Other
			TG (mg/dL)	ALT	AST	CK		
1	18, 80	[145, 250] mg/dL	350	2 ULN	2 ULN	1.5 ULN		
2	18	[145, 250] mg/dL	350	2 ULN	2 ULN			
3	18	[145, 250] mg/dL	350	2 ULN	2 ULN			
4	[18, 80]	130 mg/dL	350	1.5 ULN	1.5 ULN	1.5 ULN	CHD or CHD risk equivalent	
5	[18, 79]	> NCEP ATP III level	350	1.5 ULN	1.5 ULN	1.5 ULN		
6	18, 80	[145, 250] mg/dL	350	2 ULN	2 ULN	1.5 ULN		
7	18, 79	130 mg/dL	350	1.5 ULN	1.5 ULN	1.5 ULN		
8	18, 81	[145, 250] mg/dL	350	1.5 ULN	1.5 ULN	1.5 ULN		
9	18, 80	100 mg/dL	< 400	2 ULN	2 ULN	2 ULN	Type 2 diabetes patients	
10	18	[145, 250] mg/dL	350	2 ULN	2 ULN			
11	18	[145, 250] mg/dL	350	2 ULN	2 ULN			
12	[18, 79]	70 mg/dL patients with AVD otherwise	100 mg/dL	2 ULN	2 ULN	2 ULN	Metabolic syndrome patients	
13	18	[145, 250] mg/dL	350	2 ULN	2 ULN		Patients were African American	
14	18	> NCEP ATP III level	350	1.5 ULN	1.5 ULN	1.5 ULN	77% patients had CHD Ongoing statin	
15	18	[101, 160] mg/dL	354	1.5 ULN	1.5 ULN	1.5 ULN	CHD patients Ongoing ATORVA	
16	18	130 mg/dL	350	2 ULN	2 ULN			
17	[30, 75]	> 100 mg/dL	< 600	1.3 ULN	1.3 ULN	1.5 ULN	Type 2 diabetes patients	
18	[18, 79]	[100, 160] mg/dL	350	1.5 ULN	1.5 ULN	2 ULN	Non-diabetes patients	
19	[18, 79]	[70, 160] mg/dL	350	1.5 ULN	1.5 ULN	2 ULN		
20	18	[101, 160] mg/dL	354	1.5 ULN	1.5 ULN	1.5 ULN	CHD patients Ongoing SIMVA	
21	65	70 mg/dL patients with AVD otherwise	100 mg/dL	1.5 ULN	1.5 ULN	2 ULN	elderly patients	
22	18	[101, 160] mg/dL	354	1.5 ULN	1.5 ULN	1.5 ULN	CHD patients Ongoing SIMVA	
23	18	[101, 160] mg/dL	354	1.5 ULN	1.5 ULN	1.5 ULN	CHD patients Ongoing ATORVA	
24	18	[101, 160] mg/dL		1.5 ULN	1.5 ULN	1.5 ULN	CHD patients with type II diabetes and ongoing SIMVA	
25	[18, 79]	[100, 160] mg/dL	350	2 ULN	2 ULN	3 ULN	CHD patients Ongoing statin 6 weeks	
26	18	> NCEP ATP II level	350	2 ULN	2 ULN	1.5 ULN	Patients on statin with history of > 80% of daily doses for preceding 6 weeks	

ATORVA, atorvastatin; SIMVA, simvastatin. NCEP, National Cholesterol Education Program; ATP, Adult Treatment Panel; CHD, coronary heart disease; ULN, Upper Limit of Normal; AVD, Atherosclerotic Vascular Disease.

Table IV

Parameter estimates of the meta-regression models in the simulation study.

C-model	Parameter	True value	EST		SE		RMSE		Power (%)	
			$V = V_0$	$V_0/2$	$V_0/10$	V_0	$V_0/2$	$V_0/10$	V_0	$V_0/2$, $V_0/10$
I	1	0.1	0.099	0.099	0.100	0.035	0.026	0.016	0.048	0.037, 0.021
	2	-0.7	-0.699	-0.695	-0.698	0.253	0.187	0.110	0.329	0.247, 0.136
	3	0.6	0.590	0.591	0.596	0.216	0.162	0.098	0.286	0.219, 0.127
	4	1.0	0.987	0.987	0.992	0.271	0.206	0.120	0.358	0.274, 0.155
	11	-52	-51.23	-51.41	-51.75	15.38	11.54	7.13	20.15	15.23, 8.84
	γ_{12}^*	-12	-12.00	-12.00	-12.00	0.909	0.671	0.388	0.991	0.733, 0.418
	21	-23	-22.30	-22.49	-22.79	14.64	11.00	6.86	19.01	14.37, 8.41
	γ_{22}^*	-20	-19.98	-19.98	-19.98	1.32	0.98	0.59	1.40	1.04, 0.60
	1	0.1	0.100	0.100	0.100	0.026	0.019	0.010	0.035	0.026, 0.014
	2	-0.7	-0.706	-0.703	-0.700	0.216	0.161	0.095	0.267	0.200, 0.112
	4	1.0	0.991	0.991	0.994	0.256	0.195	0.113	0.319	0.244, 0.139
II	11	-52	-51.65	-51.81	-51.93	11.37	8.40	4.76	14.02	10.30, 5.47
	γ_{12}^*	-12	-12.01	-12.00	-12.00	0.902	0.667	0.384	0.975	0.721, 0.412
	21	-23	-22.68	-22.84	-22.96	11.28	8.35	4.83	13.77	10.19, 5.53
	γ_{22}^*	-20	-19.98	-19.98	-19.98	1.32	0.98	0.58	1.39	1.03, 0.60
	1	0.1	0.100	0.100	0.100	0.026	0.019	0.011	0.034	0.025, 0.014
	4	1.0	0.992	0.993	0.995	0.259	0.196	0.110	0.317	0.240, 0.133
	11	-52	-51.90	-51.93	-51.96	5.79	4.23	2.27	7.54	5.53, 2.86
	γ_{12}^*	-12	-12.01	-12.00	-12.00	0.904	0.668	0.385	0.975	0.721, 0.412
	21	-23	-22.96	-22.97	-22.98	4.10	3.01	1.66	5.30	3.91, 2.05
	γ_{22}^*	-20	-19.98	-19.98	-19.98	1.32	0.98	0.58	1.39	1.03, 0.60
III	1	0.1	0.100	0.100	0.100	0.026	0.019	0.011	0.034	0.025, 0.014
	4	1.0	0.992	0.993	0.995	0.259	0.196	0.110	0.317	0.240, 0.133
	11	-52	-51.90	-51.93	-51.96	5.79	4.23	2.27	7.54	5.53, 2.86
	γ_{12}^*	-12	-12.01	-12.00	-12.00	0.904	0.668	0.385	0.975	0.721, 0.412
	21	-23	-22.96	-22.97	-22.98	4.10	3.01	1.66	5.30	3.91, 2.05
	γ_{22}^*	-20	-19.98	-19.98	-19.98	1.32	0.98	0.58	1.39	1.03, 0.60
	1	0.1	0.100	0.100	0.100	0.026	0.019	0.011	0.034	0.025, 0.014
	4	1.0	0.992	0.993	0.995	0.259	0.196	0.110	0.317	0.240, 0.133
	11	-52	-51.90	-51.93	-51.96	5.79	4.23	2.27	7.54	5.53, 2.86
	γ_{12}^*	-12	-12.01	-12.00	-12.00	0.904	0.668	0.385	0.975	0.721, 0.412
	21	-23	-22.96	-22.97	-22.98	4.10	3.01	1.66	5.30	3.91, 2.05
	γ_{22}^*	-20	-19.98	-19.98	-19.98	1.32	0.98	0.58	1.39	1.03, 0.60

Note that $\gamma_{12}^* = \gamma_{12} - \gamma_{11}$ and $\gamma_{22}^* = \gamma_{22} - \gamma_{21}$.

The frequencies of ranking the true model as best, second best, and third best under AIC, AICC, and BIC.

Table V

C-Model	Ranking	AIC			AICC			BIC		
		V ₀	V ₀ /2	V ₀ /10	V ₀	V ₀ /2	V ₀ /10	V ₀	V ₀ /2	V ₀ /10
I	Best	634	862	999	363	676	996	428	721	997
	Second	90	58	0	96	84	3	100	74	2
	Third	54	22	0	71	55	0	60	46	0
	Top three	778	942	999	530	815	999	588	841	999
II	Best	573	668	726	530	752	874	524	735	848
	Second	222	240	270	170	151	122	179	164	148
	Third	57	31	2	81	30	2	72	36	2
	Top three	852	939	998	781	933	998	775	935	998
III	Best	502	535	562	613	724	799	600	690	759
	Second	135	145	194	168	135	132	160	146	138
	Third	178	178	181	84	72	51	95	79	78
	Top three	815	858	937	865	931	982	855	915	975

AIC, Akaike information criterion; AICC, corrected AIC; BIC, Bayesian information criterion.

Table VI

The values of AIC, AICC, BIC, and Q_K for the LDL-C data.

Model	AIC	AICC	BIC	Q_K
Baseline LDL-C, baseline HDL-C, duration	315.7	325.3	332.1	1545.8
Baseline LDL-C, duration	316.6	324.6	331.7	2194.1
Baseline LDL-C, baseline HDL-C, age, duration	316.6	328.0	334.3	1362.1
No covariates	318.8	324.1	331.3	3033.6

Note that the p -values associated with Q_K statistics were all < 0.0001 .

Table VII

The maximum likelihood estimates under the best AIC model for the LDL-C data.

Parameter	MLE	SE	t-value	p-value	95% CI
β_{11}	-34.060	16.224	-2.099	0.0475	(-67.705, -0.414)
$\beta_{12} - \beta_{11}$	-11.971	0.931	-12.859	<0.0001	(-13.902, -10.040)
β_{21}	3.466	16.221	0.214	0.8328	(-30.175, 37.106)
$\beta_{22} - \beta_{21}$	-19.971	1.423	-14.036	<0.0001	(-22.921, -17.020)
$(\beta_{22} - \beta_{21}) - (\beta_{12} - \beta_{11})$	-8.000	1.701	-4.704	0.0001	(-11.526, -4.373)
V_{111}	38.419	16.231	2.367	0.0272	(4.757, 72.080)
V_{112}	-12.843	7.470	-1.719	0.0996	(-28.334, 2.649)
V_{122}	9.856	4.197	2.348	0.0283	(1.151, 18.561)
V_{211}	20.047	9.398	2.133	0.0443	(0.557, 39.537)
V_{212}	-16.668	8.909	-1.871	0.0747	(-35.143, 1.807)
V_{222}	22.977	10.066	2.283	0.0325	(2.102, 43.852)
β_1 (baseline LDL-C)	0.080	0.034	2.358	0.0277	(0.010, 0.151)
β_2 (baseline HDL-C)	-0.534	0.313	-1.705	0.1022	(-1.183, 0.115)
δ (duration)	0.908	0.356	2.555	0.0181	(0.171, 1.646)