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Bayesian inference for multivariate meta-analysis Box-Cox transformation models for individual patient data with applications to evaluation of cholesterol lowering drugs

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Abstract

In this paper, we propose a class of Box-Cox transformation regression models with multidimensional random effects for analyzing multivariate responses for individual patient data (IPD) in meta-analysis. Our modeling formulation uses a multivariate normal response meta-analysis model with multivariate random effects, in which each response is allowed to have its own Box-Cox transformation. Prior distributions are specified for the Box-Cox transformation parameters as well as the regression coefficients in this complex model, and the Deviance Information Criterion (DIC) is used to select the best transformation model. Since the model is quite complex, a novel Monte Carlo Markov chain (MCMC) sampling scheme is developed to sample from the joint posterior of the parameters. This model is motivated by a very rich dataset comprising 26 clinical trials involving cholesterol lowering drugs where the goal is to jointly model the three dimensional response consisting of Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), and Triglycerides (TG) (LDL-C, HDL-C, TG). Since the joint distribution of (LDL-C, HDL-C, TG) is not multivariate normal and in fact quite skewed, a Box-Cox transformation is needed to achieve normality. In the clinical literature, these three variables are usually analyzed univariately: however, a multivariate approach would be more appropriate since these variables are correlated with each other. A detailed analysis of these data is carried out using the proposed methodology.

Keywords

Heterogeneity; Individual patient data; Markov chain Monte Carlo; Multiple trials; Random effects

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1. Introduction

Millions of Americans are struggling with high cholesterol which is well known to contribute to heart disease and other cardiovascular disease. A great deal of effort has been put forth in clinical trials studying cholesterol lowering drugs. Endpoints in such trials typically focus on one or more of three primary endpoints, these being Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), and Triglycerides (TG) (LDL-C, HDL-C, TG). In the clinical literature, these endpoints have been primarily studied and reported individually, without consideration of their joint effects and their associations within an aggregate meta-analysis framework. If one wishes to jointly model these outcomes within a meta-analysis framework and capture their joint associations, an aggregate meta-analysis framework will not suffice. In this case, an individual patient data (IPD) meta-analysis is required. Meta-analysis of IPD data is common in settings where the data analyst has access to the raw data from all the studies, as is often the case when all of the data come from the same institution or pharmaceutical company, for example. However, access to study-level data is a more common scenario than an IPD analysis since the data analyst usually has access to statistical summaries from several studies as reported in the literature. Among meta-analyses reported in the literature, univariate meta-analyses are most common primarily due to the relative simplicity and availability of software to conduct such analyses. Multivariate IPD meta-analyses are less common due to methodological challenges, complexity and lack of appropriate software. In this paper, we propose a unified framework for carrying out IPD meta-analysis for multivariate response data, which is primarily motivated by 26 clinical trials for cholesterol lowering drugs measuring (LDL-C, HDL-C, TG) as the primary outcomes of interest along with several covariates. The challenges posed here are that these response variables have very different distributions, which are not symmetric or normally distributed, and therefore one has to consider transformations on each of the 3 response variables to achieve normality.

Meta analysis of individual patient data (IPD) is a useful and effective statistical tool for synthesizing evidence across studies. It offers greater flexibility for meta-analysis and improves investigation and explanation of heterogeneity. Availability of IPD allows regression modeling for examining relationships between treatment effects and covariates that can explain the variability in terms of clinical and other factors. Whitehead et al. [1] considered IPD meta-analysis of ordinal outcomes. Their approach is based on the proportional odds model where the treatment effect is represented by the log-odds ratio. Khana et al. [2] demonstrated and highlighted the benefits of IPD meta-analysis in evaluation of diagnostic tests. Edwards et al. [3] carried out a meta-analysis using IPD to determine the analgesic efficacy and adverse effects of single-dose rofecoxib in primary dysmenorrhoea. Gorman et al. [4] conducted meta-analysis on the data from 3272 Caucasian patients with rheumatoid arthritis to examine the role of specific shared epitope genotypes in the development of rheumatoid nodules and to investigate the influence of covariates, such as disease duration and gender. Smith et al. [5] investigated heterogeneity in an IPD meta-analysis of time to event outcomes. Simmonds and Higgins [6] investigated the power of meta-regression and IPD methods to detect treatment-covariate interactions. Ziegler and

Grossarth-Maticek [7] conducted IPD meta-analysis of survival and psychosomatic self-regulation for long-term therapy of breast cancer patients with mistletoe preparation.

The Box-Cox transformation with parameter λ on a response variable *y* is defined as

$$y^* = \begin{cases} \frac{y^\lambda - 1}{\lambda} & \text{if } \lambda \neq 0, \\ \log(y) & \text{if } \lambda = 0. \end{cases}$$

The literature on Box-Cox transformations for multivariate meta-analysis is essentially non-existent. There have been a few papers that address Box-Cox transformations within a univariate meta-analysis framework, however. Lipsitz et al. [8] examined Box-Cox transformations in longitudinal data settings with missing data. Hoffmann et al. [9] used the Box-Cox transformation in analyzing dietary intake data in epidemiological studies. There have been several statistical papers addressing various issues in Box-Cox transformations, but none of these papers address Box-Cox transformations in meta-analysis settings. In addition to the classic paper by Box and Cox[10], Gurka et al. [11] examined Box-Cox transformations in linear mixed models, and Terasaka and Hosoya [12] extended the Box-Cox transformation to the multivariate time series model. Bayesian papers include [13] and [14] who examined the choice of prior distribution for the Box-Cox transformed linear model. Lee et al. [15] carried out Bayesian analysis of Box-Cox transformed linear mixed models and Gottado and Raftery [16] developed a Bayesian approach for simultaneous variable and transformation selection. Due to the complexity of Box-Cox transformation models, Bayesian methods may be preferred over the classical methods due to the recent advance in Bayesian computation and the recent development of Bayesian model comparison criteria.

In this paper, we develop a new methodology for analyzing IPD multivariate responses. Similar to trial level aggregate responses, trial random effects and trial-by-treatment random effects are incorporated into the models. Assuming the distributions of some or all of the response variables to be highly skewed, we propose a class of Box-Cox transformations for multivariate responses data within a meta-analysis framework involving IPD. Our Bayesian approach is quite innovative in the sense that we allow a different Box-Cox transformation on each response, different Box-Cox transformation parameters on each trial, coupled with a multivariate meta-regression model. The multivariate meta-regression model along with two sets of the multivariate random effects for regression coefficients and transformation parameters poses a great computational challenge. To this end, we develop novel Bayesian computational methods for fitting this model via several modified collapsed Gibbs samplers ([17],[18]). In addition, we derive the deviance information criterion for comparing several variations of the proposed multivariate meta-regression model and the Bayesian residuals for examining the goodness-of-fit of these models and demonstrate the novelty of the proposed methodology with a series of 26 clinical trials for cholesterol lowering drugs.

The rest of the paper is organized as follows. A summary and an exploratory analysis of the meta-individual patient data are presented in Section 2. The methodological development of the meta-analysis for multiple responses with Box-Cox transformations is given in Section

3. The computation algorithm to carry out Bayesian inference is developed in Section 4. The meta-data discussed in Section 2 is analyzed in detail in Section 5. We conclude the paper with brief discussion and some extensions of the proposed methodology in Section 6.

2. The Data

2.1. Description of the Data

The individual patient data used here to demonstrate the applications of our proposed models come from 26 Merck sponsored double-blind, randomized, active or placebo-controlled clinical trials on adult patients with primary hypercholesterolemia. The primary goal of these clinical trials was to evaluate the LDL-C lowering effects of Ezetimibe (which works in the digestive tract) in combination with statin (which works in the liver) in comparison to statin alone on treatment-naïve patients at baseline (on a first line therapy) and those continuing on statins at baseline (on a second line therapy). In our analyses, different statins and their doses are combined to form the "statin" and "statin+Ezetimibe" treatment groups. Ezetimibe (EZE) is available at only one dose of 10mg and the statins used in these trials included simvastatin, atorvastatin, lovastatin, rosuvastatin, pravastatin, and fluvastatin. The covariates include treatment (trt) (0 = "statin" and 1 = "statin +Ezetimibe"), baseline LDL-C (bl_ldlc), baseline HDL-C (bl_hdlc), baseline TG (bl_trig), age, race (white (reference), black, hispanic, and other), gender (Male (reference), Female), diabetes (DM, 0 = No, 1 = Yes), CHD (0 = No, 1 = Yes), body mass index (BMI), statin potency (low (reference), med (potency2), high (potency3)), and trial duration. In this analysis, we include only the patients whose covariates were available.

The meta-individual patient data considered in our analyses is a subset of the meta-data published in [19]. The citations of primary published papers in clinical journals for the 26 trials considered in this paper can be found in [19]. Leiter et al. [19] carried out a meta analysis based on the pooled data. Instead of the pooled data, we fit the meta-data via multivariate Box-Cox transformation models with multi-dimensional random effects for treatments and transformation parameters, which account for heterogeneity among the trials. A detailed summary of the covariates for these 26 clinical trials is given in Tables 1 and 2. From Tables 1 and 2, we can see a considerable amount of heterogeneity in the covariates across the trials. Specifically, the ranges of the within trial means of the continuous covariates are (89.2, 186.0), (43.1, 55.3), (127.0, 199.5), (52.3, 71.2), and (27.2, 33.6) for baseline LDL-C, baseline HDL-C, baseline TG, age and BMI, respectively. We also see drastically different proportions of the categorical covariates across trials. For example, trials 15, 17, 20, 22, 23, 24 only included CHD patients while trial 21 had no CHD patients at all. Also, there was only medium statin potency in trials 13, 15, 16, 17, 21, 23, 24, and 25 while there were no low or high statin potencies in some other studies. We further observe that the proportions of DM patients and the distributions of race were quite different across the 26 trials. This descriptive summary shows that in order to examine the treatment effects, there is a need to adjust for these covariates. More importantly, the within-trial adjustment of covariate effects may not be feasible due to the fact that the effects for some covariates are not estimable. In addition, due to the nature of the randomized trials, the within-trial adjustment of covariate effects may not be needed. This observation motivates us to develop meta-analytic regression models with common regression coefficients for the covariates across trials to adjust for heterogeneity of the covariate distributions.

2.2. Exploratory Analysis of the Data

We consider three primary outcome variables including percent changes from baseline in LDL-C, HDL-C, and TG. For ease of presentation, we simply denote these three outcome variables by LDL-C, HDL-C, and TG. For each of LDL-C, HDL-C, and TG, we first added 100 to the outcome variable to ensure it to be positive and then we fit 26 regression models, one for each trial, using all possible covariates listed above as long as they were estimable within each trial. Using the SAS procedure TRANSREG, we obtained the maximum likelihood estimates of the 26 trial-wise Box-Cox transformation parameters (λ's) for each of LDL-C, HDL-C, and TG. The boxplots of these estimates are shown in Figure 1. From this figure, we see that there is a substantial variation among the estimated transformation parameters. This variation may be partially explained by the different proportions of certain types of patients such as CHD patients across trials. For example, the estimated transformation parameters for TG were −0.37 and −0.37 for trials 15 and 20 and 0.22 and 0.33 for trials 4 and 25. From Tables 1 and 2, we see that trials 15 and 20 included only CHD patients while trials 4 and 25 had more balanced proportions of CHD patients and no CHD patients. These exploratory analyses suggest that there is a need to transform all three outcome variables and the transformation parameters vary from trial to trial.

3. Methods for Meta-analysis with Multivariate Responses and Multi-Dimensional Random Effects

3.1. The Multivariate Meta-analysis Regression Model

Consider K randomized trials, where each trial has two treatment arms ("Statin" or "Statin + EZE"), and patients in each trial were either all on statin or all not on statin prior to the trial. The sample size of the individual patient data for the k^{th} trial is n_k. Let $\boldsymbol{y}_{ik} = (y_{i1k}, \ldots, y_{iJk})'$ denote a J-dimensional vector of the responses for the i^{th} patient in the k^{th} trial. In our application, $K = 26$ and $J = 3$. Also let $\text{trt}_{ik} = 1$ if the i^{th} patient received "Statin + EZE" and 0 if "Statin" alone, and $\text{onstatin}_k = 1$ if patients were on statin and 0 if not on statin prior to the trial. Also let $\boldsymbol{x}_{ijk}$ denote a p_j-dimensional vector of covariates for the j^{th} response corresponding to the i^{th} patient.

We propose the following multivariate random effects transformation regression model for the meta-analysis:

$$g_{jk}(y_{ijk})=\boldsymbol{x}_{ijk}'\boldsymbol{\beta}_j+[\gamma_{jk0}+\gamma_{jk1}\text{trt}_{ik}]\,(1-\text{onstatin}_k)+[\gamma_{jk2}+\gamma_{jk3}\text{trt}_{ik}]\text{onstatin}_k+\varepsilon_{ijk}, \quad (3.1)$$

where $g_{jk}(.)$ is a function of y_{ijk} and $\boldsymbol{\beta}_j = (\beta_{j1}, \ldots, \beta_{jp_j})'$ is the vector of fixed effects regression coefficients corresponding to the p_j covariates. For $j = 1, \ldots, J$, we consider the Box-Cox transformation for g_{jk} as follows:

$$g_{jk}(y_{ijk})=\begin{cases} \frac{(y_{ijk}-a_j)^{\lambda_{jk}}-1}{\lambda_{jk}}, & \text{if } \lambda_{jk} \neq 0, \\ \log(y_{ijk}-a_j) & \text{if } \lambda_{jk}=0, \end{cases} \quad (3.2)$$

where a_j is a pre-specified constant such that $y_{ijk} - a_j > 0$. In our application, we take $a_j = -100$. Let $\gamma_{jk} = (\gamma_{jk0}, \gamma_{jk1}, \gamma_{jk2}, \gamma_{jk3})'$ so that γ_{jk} represents the vector of random effects in (3.1). Also let $\varepsilon_{ik} = (\varepsilon_{i1k}, \ldots, \varepsilon_{iJk})'$. We assume ε_{ik}, γ_{jk}, and λ_{jk} are independent. We further assume

$$\varepsilon_{ik} \sim N_J(0, \sum), \quad (3.3)$$

independently, for $i = 1, \ldots, n_k$ and $k = 1, \ldots, K$, where Σ is a $J \times J$ unstructured covariance matrix, which captures the dependence among the J responses $y_{i1k}, y_{i2k}, \ldots, y_{iJk}$,

$$\gamma_{jk} \sim N_4(\gamma_j, V_j), \quad (3.4)$$

where $\gamma_j = (\gamma_{j0}, \gamma_{j1}, \gamma_{j2}, \gamma_{j3})'$ denotes the vector of the overall treatment and onstatin effects for the j^{th} response, and

$$\lambda_{jk} \sim N(\lambda_j, \tau_j^2), \quad (3.5)$$

where λ_j denotes the overall parameter in the Box-Cox transformation and τ_j^2 captures the between-trial variability of the Box-Cox transformation for the j^{th} response. To ensure model identifiability, we assume

$$V_j=\begin{pmatrix} V_{j00} & V_{j01} & 0 & 0 \\ V_{j01} & V_{j11} & 0 & 0 \\ 0 & 0 & V_{j22} & V_{j23} \\ 0 & 0 & V_{j23} & V_{j33} \end{pmatrix} = \begin{pmatrix} V_j^1 & 0 \\ 0 & V_j^2 \end{pmatrix}. \quad (3.6)$$

In (3.6), V_{j00} and V_{j11} capture the variabilities of γ_{jk0} and γ_{jk1}, and V_{j01} captures the correlation between γ_{jk0} and γ_{jk1} among the trials in which patients were not on statin; and similarly, V_{j22} and V_{j33} capture the variabilities of γ_{jk2} and γ_{jk3}, and V_{j23} captures the correlation between γ_{jk2} and γ_{jk3} among the trials in which patients were on statin. A flow diagram of the proposed model specified by (3.1), (3.2), (3.3), and (3.5) is shown in Figure 2.

In our application, the y_{ijk}'s include the percent changes of LDL-C, HDL-C, and TG. The covariates include baseline LDL-C (bl_ldlc), baseline HDL-C (bl_hdlc), baseline TG (bl_trig), age, race (white (reference), black, hispanic, other), gender (female versus male), diabetes (DM), CHD, BMI, statin potency (potency2, potency3), and trial duration.

The meta-analysis regression model defined in (3.1), (3.3), and (3.4) is a multivariate random effects model that captures several sources of between-trial variation involving several treatments, while simultaneously accommodating trial level covariates. First, γ_{jk0} is the random intercept for those not on statin, and γ_{jk1} is the random effect for treatment across trials for those not on statin. Similarly, γ_{jk2} is the random intercept for those on statin, while γ_{jk3} is the random effect of treatment for those on statin. The resulting model will require estimation of the covariance matrix of the random effects, denoted by V_j, which is a block diagonal matrix. Simultaneous estimation of $(\beta_1, \ldots, \beta_J, \Sigma, \gamma_1, \ldots, \gamma_J, V_1, \ldots, V_J, \lambda_1, \ldots, \lambda_J, \tau_1^2, \ldots, \tau_J^2)$ is not trivial and requires a sophisticated and computationally intensive Gibbs sampling algorithm.

3.2. The Complete-Data Likelihood Function

Write $\boldsymbol{w}_{ik}^{\prime}=((1-\mathrm{onstatin}_k), \mathrm{trt}_{ik}\times(1-\mathrm{onstatin}_k), \mathrm{onstatin}_k, \mathrm{trt}_{ik}\times\mathrm{onstatin}_k)$ and

$$y_{ijk}^{*}\equiv g_{jk}(y_{ijk})=\frac{(y_{ijk}-a_j)^{\lambda_{jk}}-1}{\lambda_{jk}}. \quad (3.7)$$

Let

$\boldsymbol{y}_{ik}^{*}=(y_{i1k}^{*},\ldots,y_{iJk}^{*})^{\prime},\ X_{ik}=\mathrm{diag}\,(\boldsymbol{x}_{i1k}^{\prime},\ldots,\boldsymbol{x}_{iJk}^{\prime}),\ \boldsymbol{\beta}=(\boldsymbol{\beta}_1^{\prime},\ldots,\boldsymbol{\beta}_J^{\prime})^{\prime},\ W_{ik}=\mathrm{diag}(\boldsymbol{w}_{ik}^{\prime},\ \ldots,\boldsymbol{w}_{ik}^{\prime}),\ \boldsymbol{\gamma}_k^R=(\boldsymbol{\gamma}_{1k}^{\prime},\ldots,\gamma$, and $\boldsymbol{\lambda}_k^R=(\lambda_{1k},\ldots,\lambda_{Jk})^{\prime}$. Then, from (3.1) and (3.3), we have

$$\boldsymbol{y}_{ik}^{*}=X_{ik}\boldsymbol{\beta}+W_{ik}\boldsymbol{\gamma}_k^R+\boldsymbol{\varepsilon}_{ik},\boldsymbol{\varepsilon}_{ik}\sim N_J(0,\textstyle\sum).$$

Thus, given $\boldsymbol{\beta}$, $\boldsymbol{\gamma}_k^R$, Σ, and $\boldsymbol{\lambda}_k^R$, the joint density of $\boldsymbol{Y}_{ik}^{*}$ is of the form

$$f(\boldsymbol{y}_{ik}^{*}|\boldsymbol{\beta},\boldsymbol{\gamma}_k^R,\textstyle\sum,\boldsymbol{\lambda}_k^R,X_{ik},W_{ik})=\frac{|\sum|^{-1/2}}{(2\pi)^{J/2}}\exp\left\{-\frac{1}{2}(\boldsymbol{y}_{ik}^{*}-X_{ik}\boldsymbol{\beta}-W_{ik}\boldsymbol{\gamma}_k^R)^{\prime}\textstyle\sum^{-1}(\boldsymbol{y}_{ik}^{*}-X_{ik}\boldsymbol{\beta}-W_{ik}\boldsymbol{\gamma}_k^R)\right\}. \quad (3.8)$$

The Jacobian of the transformation (3.7) is given by

$$\mathscr{J}(\boldsymbol{y}_{ik}^{*}\to\boldsymbol{y}_{ik})=\prod_{j=1}^{J}(y_{ijk}-a_j)^{\lambda_{jk}-1}, \quad (3.9)$$

where $\boldsymbol{y}_{ik} = (y_{i1k}, \ldots, y_{iJk})'$. Combining (3.8) and (3.9) gives the density of $\boldsymbol{y}_{ik}$, which takes the form:

$$\begin{aligned}&f(\boldsymbol{y}_{ik}|\boldsymbol{\beta},\boldsymbol{\gamma}_k^R,\textstyle\sum,\boldsymbol{\lambda}_k^R,X_{ik},W_{ik})\\&=\frac{|\sum|^{-1/2}}{(2\pi)^{J/2}}\exp\left\{-\frac{1}{2}(\boldsymbol{y}_{ik}^{*}-X_{ik}\boldsymbol{\beta}-W_{ik}\boldsymbol{\gamma}_k^R)^{\prime}\textstyle\sum^{-1}(\boldsymbol{y}_{ik}^{*}-X_{ik}\boldsymbol{\beta}-W_{ik}\boldsymbol{\gamma}_k^R)\right\}\prod_{j=1}^{J}(y_{ijk}-a_j)^{\lambda_{jk}-1}.\end{aligned} \quad (3.10)$$

Further, the complete-data likelihood function is given by

$$L(\boldsymbol{\beta},\sum,\boldsymbol{\gamma}^R,\boldsymbol{\gamma},V,\boldsymbol{\lambda}^R,\boldsymbol{\lambda},\boldsymbol{\tau}^2|D_{obs})=\prod_{k=1}^{K}\left\{\left[\prod_{i=1}^{n_k}f(\boldsymbol{y}_{ik}|\boldsymbol{\beta},\boldsymbol{\gamma}_k^R,\sum,X_{ik},W_{ik})\right]\times\left[\prod_{j=1}^{J}(2\pi)^{-\frac{4}{2}}|V_j|^{-\frac{1}{2}}\exp\left\{-\frac{1}{2}(\boldsymbol{\gamma}_{jk}-\boldsymbol{\gamma}_j)'V_j^{-1}(\boldsymbol{\gamma}_{jk}-\boldsymbol{\gamma}_j)\right\}\right]\times\left[\prod_{j=1}^{J}(2\pi\tau_j^2)^{-\frac{1}{2}}\exp\left\{-\frac{1}{2\tau_j^2}(\lambda_{jk}-\lambda_j)^2\right\}\right]\right\}, \quad (3.11)$$

where $f(\boldsymbol{y}_{ik}|\boldsymbol{\beta},\boldsymbol{\gamma}_k^R,\sum,\boldsymbol{\lambda}_k^R,X_{ik},W_{ik})$ is defined by (3.10), $\boldsymbol{\gamma}^R=((\boldsymbol{\gamma}_1^R)',\dots,(\boldsymbol{\gamma}_K^R)')'$, $\boldsymbol{\gamma}=(\boldsymbol{\gamma}_1',\dots,\boldsymbol{\gamma}_K')'$, $V = \mathrm{diag}(V_1, \dots, V_J)$, $\boldsymbol{\lambda}^R=((\boldsymbol{\lambda}_1^R)',\dots,(\boldsymbol{\lambda}_K^R)')'$, $\boldsymbol{\lambda} = (\lambda_1, \dots, \lambda_J)'$, and $\boldsymbol{\tau}^2=(\tau_1^2,\dots,\tau_J^2)'$.

3.3. Prior and Posterior

We assume that $\boldsymbol{\beta}$, Σ, $\boldsymbol{\gamma}$, V, $\boldsymbol{\lambda}$, and $\boldsymbol{\tau}^2$ are independent *a priori*. Thus, the joint prior for ($\boldsymbol{\beta}$, Σ, $\boldsymbol{\gamma}$, V, $\boldsymbol{\lambda}$, and $\boldsymbol{\tau}^2$) is of the form

$$\pi(\boldsymbol{\beta},\sum,\boldsymbol{\gamma},V,\boldsymbol{\lambda},\boldsymbol{\tau}^2)=\pi(\boldsymbol{\beta})\pi(\sum)\pi(\boldsymbol{\gamma})\pi(V)\pi(\boldsymbol{\lambda})\pi(\boldsymbol{\tau}^2). \quad (3.12)$$

We further assume $\boldsymbol{\beta} \sim N_p(0, c_{01}I_p)$, where $p=\sum_{j=1}^{J}p_j$, $\boldsymbol{\gamma} \sim N_{4J}(0, c_{02}I_{4J})$, $\boldsymbol{\lambda} \sim N_J(0, c_{03}I_J)$, $\Sigma^{-1} \sim \text{Wishart}_J(d_0, S_0)$, $V_j^{h^{-1}}\sim\text{Wishart}_2(a_0,V_0^h)$ for $h = 1, 2$ and $j = 1, \dots, J$, and $\tau_j^2\sim\text{IG}(b_{01},b_{02})$ for $j = 1, \dots, J$, where c_{01}, c_{02}, c_{03}, d_0, S_0, a_0, V_0^1, V_0^2, b_{01}, and b_{02} are prespecified hyperparameters. Further, we have

$\pi(\sum^{-1}|d_0,S_0)\propto|\sum^{-1}|^{(d_0-J-1)/2}\exp\left(-\frac{1}{2}\mathrm{tr}\,(S_0^{-1}\sum^{-1})\right)$ and $p(\tau_j^2|b_{01},b_{02})\propto(\tau_j^2)^{-(b_{01}+1)}\exp(-b_{02}/\tau_j^2)$ for $j = 1, \dots, J$. Although independent normal priors are specified for $\boldsymbol{\beta}$, $\boldsymbol{\gamma}$, and $\boldsymbol{\lambda}$, multivariate normal priors may also be specified. However, when c_{01}, c_{02}, and c_{03} are large, independent normal priors are adequate since we essentially specify non-informative priors for $\boldsymbol{\beta}$, $\boldsymbol{\gamma}$, and $\boldsymbol{\lambda}$. Using (3.11) and (3.12), the posterior distribution is given by

$$\pi(\boldsymbol{\beta},\sum,\boldsymbol{\gamma}^R,\boldsymbol{\gamma},V,\boldsymbol{\lambda}^R,\boldsymbol{\lambda},\boldsymbol{\tau}^2|D_{obs})\propto L(\boldsymbol{\beta},\sum,\boldsymbol{\gamma}^R,\boldsymbol{\gamma},V,\boldsymbol{\lambda}^R,\boldsymbol{\lambda},\boldsymbol{\tau}^2|D_{obs})\pi(\boldsymbol{\beta},\sum,\boldsymbol{\gamma},V,\boldsymbol{\lambda},\boldsymbol{\tau}^2). \quad (3.13)$$

3.4. Model Comparison via DIC

Let

$\boldsymbol{\lambda}_k^R=(\lambda_{1k},\dots,\lambda_{Jk})'$, $\boldsymbol{y}_k=(\boldsymbol{y}_{1k}',\dots,\boldsymbol{y}_{n_k,k}')'$, $\boldsymbol{y}_k^*=((\boldsymbol{y}_{1k}^*)',\dots,(\boldsymbol{y}_{n_k,k}^*)')'$, $X_k=(X_{1k}',\dots,X_{n_k,k}')'$, and $W_k=(W_{1k}',\dots,W_{n_k,k}')'$. Write $\boldsymbol{\psi} = (\boldsymbol{\beta}, \boldsymbol{\gamma}, \Sigma, V, \boldsymbol{\lambda}^R)$. We define the deviance function as follows

$$D(\boldsymbol{\psi}) = -2\sum_{k=1}^{K}\log\left(f(\boldsymbol{y}_k|\boldsymbol{\beta},\boldsymbol{\gamma},\sum,V,\boldsymbol{\lambda}_k^R,X_k,W_k)\right), \quad (3.14)$$

where $f(\boldsymbol{y}_k|\boldsymbol{\beta},\boldsymbol{\gamma},\sum,V,\boldsymbol{\lambda}_k^R,X_k,W_k)$ is the marginal distribution of $\boldsymbol{y}_k$, which is given in Appendix A. Then, the Deviance Information Criterion (DIC) proposed by Spiegelhalter et al. [20] is given by

$$\mathrm{DIC} = D(\overline{\boldsymbol{\psi}}) + 2p_D, \quad (3.15)$$

where $\bar{\psi} = E[\psi|D_{obs}]$ and $p_D = E[D(\psi)|D_{obs}] - D(\bar{\psi})$, which is the effective number of model parameters.

We will use DIC to compare the following three models:

- $\mathcal{M}_1$ $\lambda_{jk} = 1$ for $j = 1, \ldots, J$ and $k = 1, \ldots, K$ (no transformation model);
- $\mathcal{M}_2$ $\lambda_{jk} = \lambda_j$ for $j = 1, \ldots, J$ and $k = 1, \ldots, K$ (fixed transformation parameters model); and
- $\mathcal{M}_3$ random λ_{jk} for $j = 1, \ldots, J$ and $k = 1, \ldots, K$ (random transformation parameters model).

4. Computational Development

We consider the following one-to-one transformations:

$\boldsymbol{\gamma}_k^{*R} = (\boldsymbol{\gamma}^{*'}_{1k}, \boldsymbol{\gamma}^{*'}_{2k}, \ldots, \boldsymbol{\gamma}^{*'}_{Jk})' = \boldsymbol{\gamma}_k^R - \boldsymbol{\gamma}$ for $k = 1, \ldots, K$. Thus, $\gamma^*_{jk} = \gamma_{jk} - \gamma_j$ for $j = 1, \ldots, J$ and $k = 1, \ldots, K$. Write $\boldsymbol{\gamma}^{*R} = ((\boldsymbol{\gamma}_1^{*R})', \ldots, (\boldsymbol{\gamma}_K^{*R})')'$. Also, let $X_{ik}^* = (X_{ik}, W_{ik})$ for $i = 1, \ldots, n$ and $k = 1, \ldots, K$ and $\theta = (\beta', \gamma')'$. Then, we have

$$\begin{aligned}
&\pi(\boldsymbol{\theta},\sum,\boldsymbol{\gamma}^{*R},V,\boldsymbol{\lambda}^R,\boldsymbol{\lambda},\boldsymbol{\tau}^2|D_{obs})\\
&\propto \prod_{k=1}^{K}\prod_{i=1}^{n_k}|\sum|^{-\frac{1}{2}}\exp\left\{-\tfrac{1}{2}(\boldsymbol{y}_{ik}^*-X_{ik}^*\boldsymbol{\theta}-W_{ik}\boldsymbol{\gamma}_k^{*R})'\sum^{-1}(\boldsymbol{y}_{ik}^*-X_{ik}^*\boldsymbol{\theta}-W_{ik}\boldsymbol{\gamma}_k^{*R})\right\}\\
&\times\prod_{k=1}^{K}\prod_{i=1}^{n_k}\prod_{j=1}^{J}(y_{ijk}-a_j)^{\lambda_{jk}-1}\times\prod_{k=1}^{K}\prod_{j=1}^{J}|V_j|^{-\frac{1}{2}}\exp\left(-\tfrac{1}{2}(\boldsymbol{\gamma}_{jk}^*)'V_j^{-1}\boldsymbol{\gamma}_{jk}^*\right)\\
&\times\prod_{k=1}^{K}\prod_{j=1}^{J}|\tau_j^2|^{-\frac{1}{2}}\exp\left\{-\tfrac{1}{2\tau_j^2}(\lambda_{jk}-\lambda_j)^2\right\}\times\exp\left(-\tfrac{\boldsymbol{\beta}'\boldsymbol{\beta}}{2c_{01}}\right)\times\exp\left(-\tfrac{\boldsymbol{\gamma}'\boldsymbol{\gamma}}{2c_{02}}\right)\\
&\times\exp\left(-\tfrac{\boldsymbol{\lambda}'\boldsymbol{\lambda}}{2c_{03}}\right)\times|\sum^{-1}|^{(d_0-J-1)/2}\exp\left\{-\tfrac{1}{2}\mathrm{tr}\left(S_0^{-1}\sum^{-1}\right)\right\}\\
&\times\prod_{j=1}^{J}\prod_{h=1}^{2}|V_j^h|^{-\frac{a_0-2-1}{2}}\exp\left\{-\tfrac{1}{2}\mathrm{tr}\left(V_0^{h-1}V_j^{h-1}\right)\right\}\times\prod_{j=1}^{J}(\tau_j^2)^{-(b_{01}+1)}\exp(-b_{02}/\tau_j^2).
\end{aligned} \quad (4.1)$$

Although an analytical evaluation of the above posterior distribution is not possible, the proposed model allows us to develop an efficient Gibbs sampling algorithm in Appendix B to sample from the joint posterior distribution in (4.1).

5. Analysis of the Meta Individual Patient Data

In this section, we present a detailed analysis of the meta individual patient data discussed in Section 2. In the following discussion, these meta-data will be referred to as MIPD. In (3.1), $\boldsymbol{x}_{ijk}$ consists of 14 covariates, including bl_ldlc, bl_hdlc, bl_tg, BMI, age, duration, Female, DM, CHD, potency2, potency3, black, hispanic, and other. The outcome variables were LDL-C, HDL-C, and TG, which were defined as percent changes from baseline in LDL-C, HDL-C, and TG. We model these three outcome variables jointly via (3.1) to (3.6) with J = 3 and K = 26. The hyperparameters of the prior in (3.12) were specified as c_{01} = 1000, c_{02} = 1000, c_{03} = 1000, $d_0 = J + 0.01$, S_0 = 0.01, a_0 = 2.01, $V_0^1=0.01, V_0^2=0.01$, b_{01} = 0.1, and b_{02} = 0.1. In all of the analyses, we standardized all of fourteen covariates, in which each covariate was subtracted from its sample mean and divided by its sample standard deviation computed using the pooled data, for numerical stability in the posterior computation.

We fit the three models discussed in Section 3.4 to the MIPD. These three models differ only in the transformation parameters. For the MIPD, the values of $\overline{D(\psi)}$, p_D, and DIC were 540,908.78, 72.88, and 541,054.53 for model $\mathcal{M}_1$; 528,295.55, 70.83, and 528,437.22 for model $\mathcal{M}_2$; and 526,891.09, 122.21, and 527,135.51 for model $\mathcal{M}_3$. Although model $\mathcal{M}_3$ has the largest p_D value, it has the smallest values of $\overline{D(\psi)}$ and DIC. The no transformation model, i.e., $\mathcal{M}_1$, has the largest DIC value. These DIC values indicate that (i) the transformation model with random λ_{jk} did fit the data better than the transformation model with fixed λ_{jk}, which implies that the transformation parameters vary from trial to trial; and (ii) both the transformation models fit the data better than the no transformation model.

To further examine the goodness-of-fit of these three models, we computed Bayesian residuals, which were defined as $r_{ijk}=E[(g_{ijk}(y_{ijk})|D_{obs})]-E[(x_{ijk}'\boldsymbol{\beta}+\boldsymbol{w}_{ik}'\boldsymbol{\gamma}_j)|D_{obs}]$, where $g_{ijk}(y_{ijk})$ is given in (3.2), $\boldsymbol{w}_{ik}'$ is defined in Section 3.2, and the expectation is taken with respect to the posterior distribution in (3.13). The boxplots of these Bayesian residuals for each of the three outcome variables under models $\mathcal{M}_1$ to $\mathcal{M}_3$ are shown in Figure 3. From Figure 3, we see that the Bayesian residuals under both the models $\mathcal{M}_2$ and $\mathcal{M}_3$ are much more symmetric and smaller than those under model $\mathcal{M}_1$. Figure 3 also shows that both models $\mathcal{M}_2$ and $\mathcal{M}_3$ had a great improvement in the residuals for the outcome variable TG over model $\mathcal{M}_1$. These results were consistent with the ones obtained based on the DIC criterion, which further confirms the need of transformations for all three outcome variables.

The posterior estimates, including the posterior means, posterior standard deviations (SDs), and 95% highest posterior density (HPD) intervals of the parameters under model $\mathcal{M}_3$ are reported in Table 3. From this table, we see that baseline LDL-C and baseline TG were significant for the percent change from baseline in LDL-C with 95% HPD intervals (−0.092, −0.067) and (0.006, 0.019), which do not include 0; baseline HDL-C and baseline TG were significant for the percent change from baseline in HDL-C with 95% HPD intervals (−0.090, −0.052) and (0.022, 0.041); and only baseline TG was significant for the percent change from baseline in TG with 95% HPD interval (−0.131, −0.107). In addition, BMI was significant only for the percent changes from baseline in HDL-C and TG with 95% HPD intervals (−0.028, −0.014) and (0.013, 0.023), and age was significant for all three outcome

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variables. The other significant covariates were gender, statin potency, and race for the percent change from baseline in LDL-C; gender, DM, CHD, and race for the percent change from baseline in HDL-C; and gender, statin potency, and race for the percent change from baseline in TG. The trial duration was not significant for all three outcome variables.

Based on the signs of the coefficients of significant terms in the fitted model, we can conclude the following concerning the directions of percent changes in LDL-C, HDL-C, and TG. First, increase in bl_ldlc, age, and potency results into higher percent reduction in LDL-C from baseline. Also, there is a higher percent reduction in LDL-C from baseline for DM (vs. non-DM), white (vs. black and vs. hispanic) while an increase in bl_trig results into a lower percent reduction in LDL-C from baseline. Second, increase in bl_hdlc and BMI results into lower percent increase in HDL-C from baseline. There is a lower percent increase in HDL-C from baseline for DM (vs. non-DM), CHD (vs. non-CHD), black (vs. white) and hispanic (vs. white) while an increase in bl_trig and age results into a higher percent increase in HDL-C from baseline. Third, increase in bl_trig, age, and potency results into higher percent reduction in TG from baseline. Also, there is a higher percent reduction in TG from baseline for black (vs. white), white (vs. hispanic) and male (vs. female) while an increase in BMI results into a lower percent reduction in TG from baseline. The above mentioned directions in percent changes in LDL-C, HDL-C and TG corresponding to changes in covariates are consistent with what we observed in our previous univariate pooled modeling without any transformation.

The results shown in Table 3 under model $\mathcal{M}_3$ further indicate that patients on “statin + EZE” had significantly more percent changes from baseline in both LDL-C and TG than those on statin alone in both first and second line therapy studies. We note here that a posterior estimate is considered to be statistically significant at a significance level of 0.05 if the corresponding 95% HPD interval does not contain 0. the significance of the regression coefficients, that is, whether the 95% HPD interval contains 0 or not. The corresponding 95% HPD intervals were (−0.476, −0.335) in the first line therapy and (−0.583, −0.358) in the second line therapy for the percent change from baseline in LDL-C; and (−0.125, −0.059) in the first line therapy and (−0.130, −0.059) in the second line therapy for the percent change from baseline in TG. However, the significant improvement with a 95% HPD interval (0.018, 0.084) in HDL-C from baseline for patients on “statin + EZE” over those on statin alone only was observed only in the first line therapy studies. From Table 3, we also see that the 95% HPD intervals for λ_1, λ_2, and λ_3 were (0.078, 0.178), (0.132, 0.267), and (−0.032, 0.054), respectively, which implies that all three outcome variables require transformations in order to achieve normality. Figure 4 shows the marginal posterior densities for these three transformation parameters. These marginal posterior densities appear to be unimodal and symmetric. Furthermore, the 95% HPD intervals of the standard deviations of the λ_{jk}'s were (0.074, 0.131) for τ_1, (0.069, 0.122) for τ_2, and (0.070, 0.122) for τ_3. The posterior estimates of the τ_j's indicate that there was substantial heterogeneity in the transformation parameters across the trials, which further explains why model $\mathcal{M}_3$ fit the MIPD better than model $\mathcal{M}_2$. In addition, the posterior estimates of Σ under model $\mathcal{M}_3$ are given in Table 4. From this table, we see that there were moderate correlations among these three outcome variables. In particular, the percent change from baseline in LDL-C was positively correlated with both the percent changes from baseline in HDL-C and TG while the percent change from baseline in HDL-C was negatively correlated with the percent change from baseline in TG.

Finally, we compare the posterior estimates of the model parameters under model $\mathcal{M}_3$ to those under model $\mathcal{M}_1$ shown in Tables 5 and 6. The noticeable differences of the posterior estimates between models $\mathcal{M}_1$ and $\mathcal{M}_3$ are the 95% HPD intervals of β_{12}, β_{17}, and β_{39}, corresponding to covariates bl_hdlc, Female, and CHD. The 95% HPD intervals of β_{12}, β_{17}, and β_{39} were (−0.531, −0.021), (0.134, 0.604), and (0.040, 1.022) under model $\mathcal{M}_1$ and (−0.012, 0.001), (−0.001, 0.011), and (−0.002, 0.009) under model $\mathcal{M}_3$. Thus, bl_hdlc and Female were two significant predictors for LDL-C and CHD was a significant predictor for TG under model $\mathcal{M}_1$ while these covariates were not significant under the best model $\mathcal{M}_3$. Although the results under $\mathcal{M}_2$ are not reported here, the posterior estimates of the parameters under model $\mathcal{M}_2$ were similar to those under model $\mathcal{M}_3$ and these two models consistently yield the same set of significant covariates. We also note that the absolute values of the posterior estimates of the correlations, $\rho_{jj'}$s, between the three outcome variables LDL-C, HDL-C, and TG under model $\mathcal{M}_1$ were consistently smaller than those under model $\mathcal{M}_3$. We further considered the univariate fixed transformation parameters model, namely, $\mathcal{M}_2^*$: $\lambda_{jk} = \lambda_j$ for $j = 1, \ldots, J$ and $k = 1, \ldots, K$ and Σ is a diagonal matrix. The values of $D(\psi)$, p_D, and DIC under this model were 530,675.97, 68.62, and 530,813.20. Thus, model $\mathcal{M}_2$ did fit the data better than $\mathcal{M}_2^*$, indicating that the correlations among three outcome variables cannot be ignored. Comparing the posterior estimates of the model parameters under model $\mathcal{M}_2^*$ shown in Table A.1 to those under model $\mathcal{M}_3$ shown in Table 3, we see some noticeable differences. Specifically, the 95% HPD intervals of β_{39}, corresponding to covariate CHD for TG, and V_{201}, corresponding to the covariance between γ_{2k0} and γ_{2k1} for HDL-C, were (0.0006, 0.0101) and (−0.0032, −0.0003) under model $\mathcal{M}_2^*$ and (−0.002, 0.009) and (−0.022, 0.013) under model $\mathcal{M}_3$. Thus, CHD was a significant predictor for TG and there was a significant correlation between γ_{2k0} and γ_{2k1} for HDL-C under model $\mathcal{M}_2^*$ while CHD and V_{201} were not significant under the best model $\mathcal{M}_3$. These results indicate that the model without transformation or the univariate fixed transformation parameters model may understate the size of dependence among the outcome variables as well as potentially incorrectly identify the association between the outcome variables and covariates, yielding a misleading conclusion in terms of the clinical importance of covariates.

In all the Bayesian computations, we used 20,000 Gibbs samples, which were taken from every fifth iteration, after a burn-in of 4,000 iterations for each model, to compute all the posterior estimates, including posterior means, posterior SDs, 95% HPD intervals, and DICs. The convergence of the Gibbs sampling algorithm was checked using several diagnostic procedures discussed in [18]. The Gibbs sampling algorithm converged much earlier than 4,000 iterations for all the parameters under the three models considered in this section. The HPD intervals were computed via the Monte Carlo method developed by Chen and Shao [21]. Computer code was written for the FORTRAN 95 compiler, and we used IMSL subroutines with double precision accuracy. The FORTRAN code is available from the authors upon request.

6. Discussion

In this paper, we have proposed a multivariate response Box-Cox regression model for modeling individual level patient data in meta-analysis and developed an efficient Gibbs sampling algorithm via the collapsed Gibbs technique of Liu (1994) to carry out the challenging posterior computation due to the large size of the meta-data and high-dimensions of the random effects. As was seen from the analysis of the (LDL-C, HDL-C, TG) data, the proposed model is quite useful and highly needed since the outcome measures have skewed distributions and appropriate transformations are needed for modeling. In all of our analyses, we demonstrated that the best fitting model is the model for which random transformations are needed. Our proposed model provides a first attempt at modeling multivariate IPD data within a Box-Cox framework.

As discussed in Section 5, the directions of the regression coefficients as well as the treatment effects under the transformation model are consistent with those in our previous univariate pooled modeling without any transformation. However, the point estimates after transformation are difficult to interpret. This is perhaps one of the major challenges with the transformation model. One possible solution to this challenge is to transform the point estimates under the transformed outcome variable to the ones under the original scale of the outcome variable. To this end, we consider the transformation $h_j(b)=\lambda_j^{1/\lambda_j}\left[b+\frac{1}{\lambda_j}\right]^{1/\lambda_j}+a_j$. Using the first-order Taylor expansion, we obtain $h_j(b) \approx h_j(b_{0j})+h_j^{'}(b_{0j})(b-b_{0j})$, where $h_j^{'}(b_{0j})=\lambda_j^{1/\lambda_j-1}\left(b_{0j}+\frac{1}{\lambda_j}\right)^{1/\lambda_j-1}$ and b_{0j} is a fixed value. Let $b_j = \boldsymbol{x}'\beta_j + [\gamma_{j0} + \gamma_{j1}\text{trt}](1 - \text{onstatin}) + [\gamma_{j2} + \gamma_{j3}\text{trt}]\text{onstatin}$ for $j = 1, 2, 3$. Based on the above approximation, the regression coefficients and treatment effects except for intercepts in the original scale are approximately the point estimates under the transformation model multiplied by $h_j^{'}(b_{0j})$. We took b_{0j} to be the average of $\boldsymbol{x}'\beta_j + [\gamma_{j0} + \gamma_{j1}\text{trt}](1 - \text{onstatin}) + [\gamma_{j2} + \gamma_{j3}\text{trt}]\text{onstatin}$ over all observed data points evaluated at the posterior means of (β_j, γ_j) and used the posterior estimate of λ_j for computing $h_j^{'}(b_{0j})$. Then, the approximate values of $\hat{\gamma}_{j1}$ and $\hat{\gamma}_{j3}$ in the original scale were −15.20 and −17.61 for LDL-C, 2.08 and 0.96 for HDL-C, and −7.11 and −7.50 for TG and these values were in a similar scale as those given in Table 5. Also, using the same approach, for HDL-C, the approximate values of $(\hat{\beta}_{22}, \hat{\beta}_{23}, \hat{\beta}_{24}, \hat{\beta}_{25}, \hat{\beta}_{27}, \hat{\beta}_{28}, \hat{\beta}_{29}, \hat{\beta}_{2,12}, \hat{\beta}_{2,13})$ in the original scale, which were significant based on their 95% HPD intervals, were (−2.87, 1.29, −0.83, 0.67, 0.54, −0.62, −0.33, −0.37, −0.29). These values were very close to (−2.86, 1.31, −0.88, 0.61, 0.57, −0.65, −0.33, −0.42, −0.28) given in Table 5.

A caution applicable to meta-analysis is worth noting here. There are always vagaries of the individual trials that lead to particularities in the analysis, and there are variations in reporting (e.g., of non-significant associations or covariates) that make external analysis conducted by third parties difficult and perhaps misleading. This is an important issue in IPD meta-analysis and must be treated with care; indeed, it may be exacerbated in multivariate analysis. In addition, there should be a sufficiently large sample size within each trial and a sufficiently large number of trials in order to estimate various random effects in the proposed model.

One of the future research work is to develop a more refined computational algorithm to transform the point estimates under the transformation model to the ones in the original scale of the outcome variable. Other future work in this area includes analyzing multivariate aggregate meta-data. In this case, several additional challenges arise in modeling and estimating the correlations between the multivariate outcome measure, as well as appropriately defining the aggregate regression model and Box-Cox transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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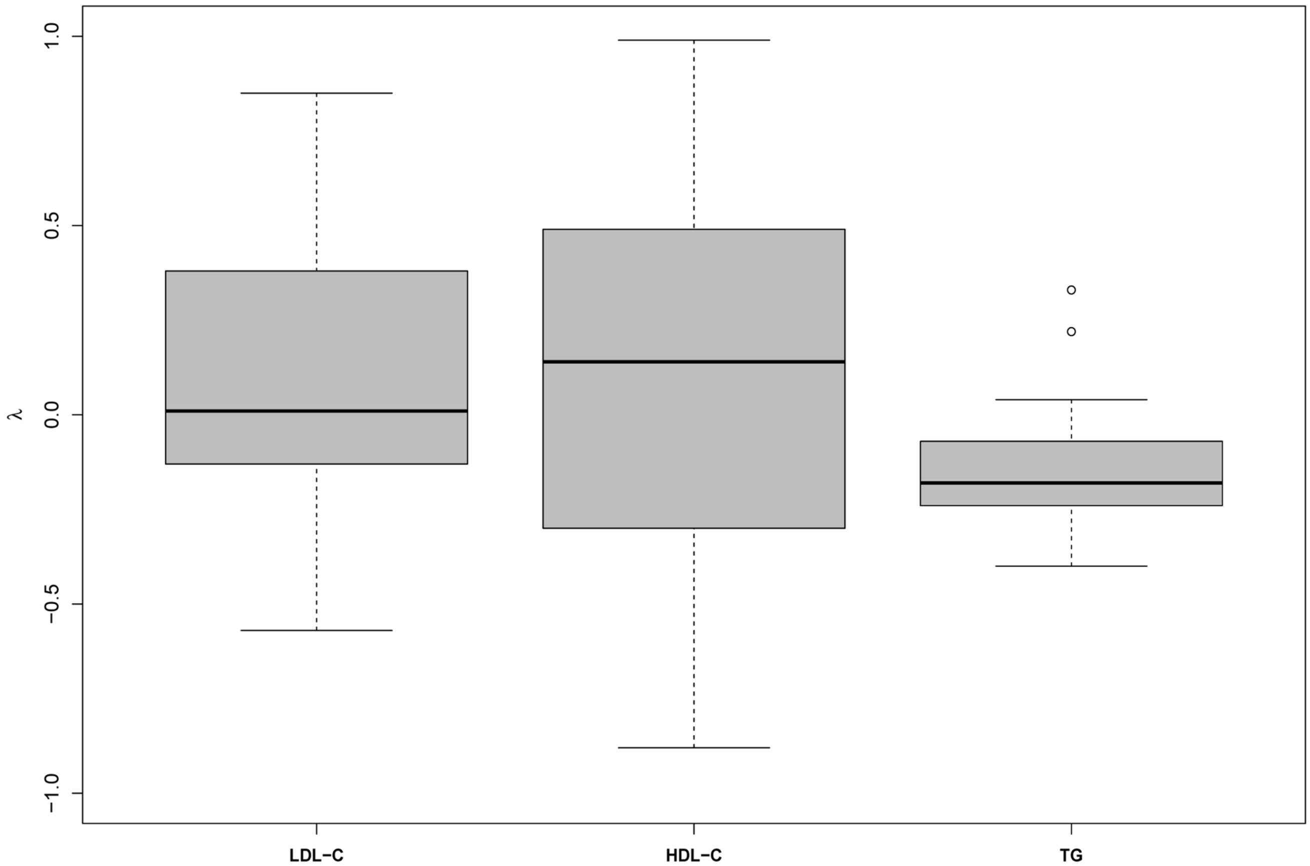

Figure 1.
Boxplots of the maximum likelihood estimates of Box-Cox transformation parameters (λ's) for LDL-C, HDL-C, and TG.

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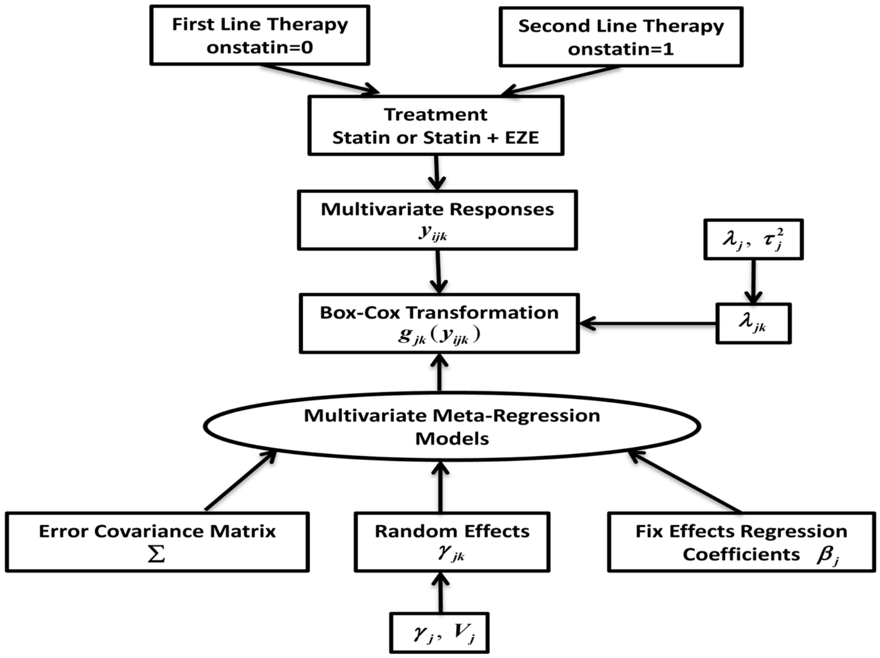

Figure 2.

A flow diagram of the proposed model.

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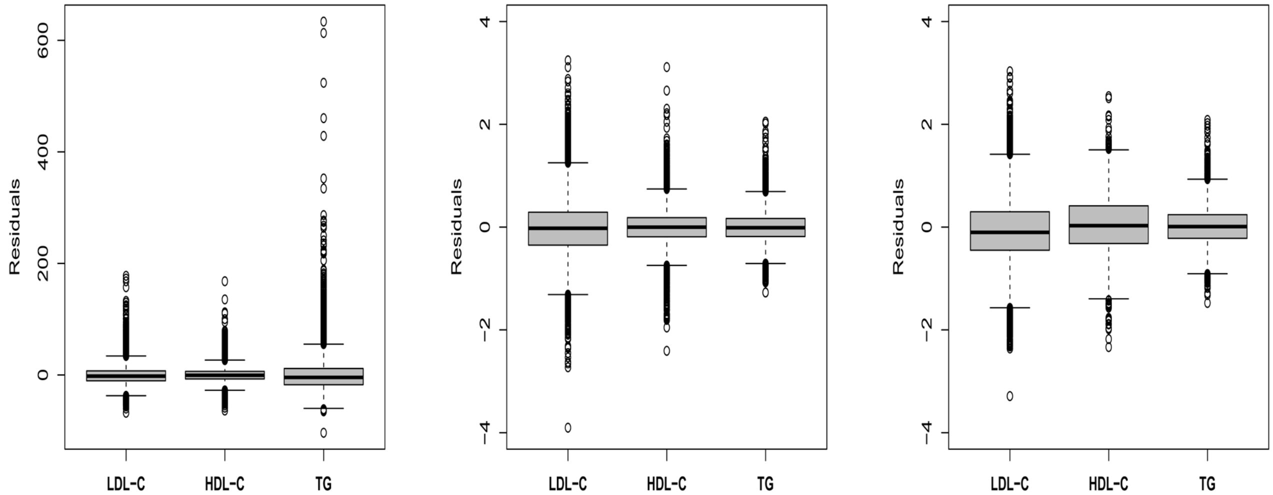

(a) model $\mathcal{M}_1$ (b) model $\mathcal{M}_2$ (c) model $\mathcal{M}_3$

Figure 3.

Boxplots of Bayesian residuals for LDL-C, HDL-C, and TG.

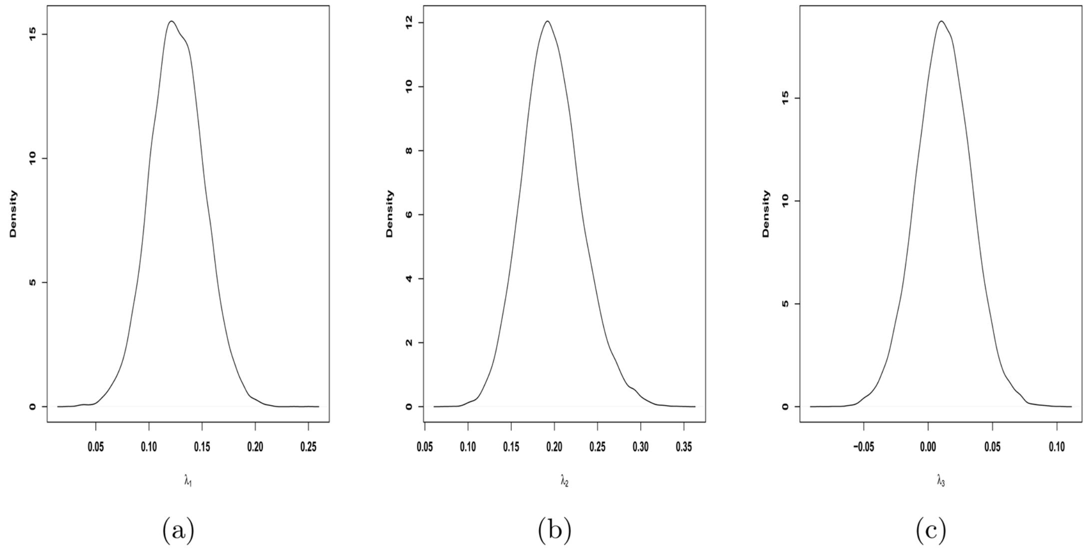

Figure 4.

Plots of the marginal posterior densities of the λ_j's under model $\mathcal{M}_3$.

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Table 1

Summary of the Covariates for the First Line Studies

Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
1	0	174.6 (25.4)	50.0 (12.1)	175.7 (70.9)	56.0 (11.1)	white	567	M	336	No	656	No	647	28.1 (4.9)	low	165	12
	345					black	24	F	359	Yes	39	Yes	48		med	353	
	1					hispanic	64								high	177	
	350					other	40										
2	0	177.4 (21.7)	50.7 (11.6)	176.9 (60.5)	56.0 (12.0)	white	348	M	182	No	382	No	375	29.5 (5.8)	low	271	12
	203					black	23	F	225	Yes	25	Yes	32		med	136	
	1					hispanic	25								high	0	
	204					other	11										
3	0	178.7 (20.0)	50.7 (11.6)	173.9 (62.8)	57.2 (12.3)	white	476	M	230	No	512	No	308	28.6 (4.9)	low	137	12
	260					black	23	F	298	Yes	16	Yes	220		med	265	
	1					hispanic	22								high	126	
	268					other	7										
4	0	168.9 (38.7)	45.5 (10.7)	184.2 (68.1)	62.2 (9.9)	white	569	M	437	No	359	No	232	31.0 (6.1)	low	240	5
	246					black	58	F	252	Yes	330	Yes	457		med	449	
	1					hispanic	57								high	0	
	443					other	5										
5	0	179.7 (42.8)	46.8 (11.5)	192.9 (84.6)	60.2 (10.4)	white	676	M	389	No	597	No	588	29.4 (5.8)	low	251	6
	248					black	33	F	357	Yes	149	Yes	158		med	495	
	1					hispanic	22								high	0	
	498					other	15										
6	0	177.3 (24.3)	51.9 (12.8)	164.1 (64.1)	55.7 (11.1)	white	868	M	487	No	931	No	843	28.1 (4.9)	low	250	12
	491					black	29	F	502	Yes	58	Yes	146		med	493	
	1					hispanic	14								high	246	
	498					other	78										

Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
7	0	178.4 (37.9)	48.9 (12.3)	183.9 (79.2)	58.7 (10.4)	white	1590	M	959	No	1435	No	1480	30.0 (5.5)	low	230	6
	924					black	142	F	888	Yes	412	Yes	367		med	933	
	1					hispanic	83								high	684	
	923					other	32										
8	0	173.0 (24.5)	50.2 (12.1)	170.2 (70.4)	55.6 (10.3)	white	2456	M	1254	No	2466	No	2592	29.6	low	0	6
	1418					black	188	F	1575	Yes	363	Yes	237	(5.8)	med	1413	
	1					hispanic	116								high	1416	
	1411					other	69										
9	0	145.4 (31.2)	45.8 (11.0)	193.7 (82.9)	59.6 (10.3)	white	876	M	566	No	1	No	1012	33.6 (7.3)	low	0	6
	714					black	143	F	627	Yes	1192	Yes	181		med	953	
	1					hispanic	110								high	240	
	479					other	64										
10	0	178.3 (20.4)	50.4 (12.4)	175.4 (61.5)	56.1 (11.6)	white	362	M	172	No	378	No	375	29.1 (5.2)	low	271	12
	218					black	27	F	237	Yes	31	Yes	34		med	138	
	1					hispanic	19								high	0	
	191					other	1										
11	0	181.7 (22.3)	52.2 (12.6)	171.5 (64.3)	58.3 (11.6)	white	424	M	200	No	470	No	452	28.2 (4.5)	low	0	12
	246					black	26	F	298	Yes	28	Yes	46		med	247	
	1					hispanic	28								high	251	
	252					other	20										
12	0	138.3 (33.7)	43.1 (10.6)	199.5 (92.4)	59.2 (9.5)	white	814	M	611	No	490	No	870	32.3 (6.2)	low	0	6
	644					black	69	F	469	Yes	590	Yes	210		med	863	
	1					hispanic	0								high	217	
	436					other	197										
13	0	175.8 (22.9)	53.0 (14.3)	137.4 (60.7)	54.5 (11.5)	white	0	M	95	No	201	No	222	31.2 (5.8)	low	0	12
	123					black	247	F	152	Yes	46	Yes	25		med	247	

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Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
	1					hispanic	0								high	0	
	124					other	0										

Table 2

Summary of the Covariates for the Second Line Studies

Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
14	0	129.1 (30.0)	48.6 (11.6)	167.3 (78.5)	62.0 (11.3)	white	2366	M	1503	No	1761	No	1570	30.6 (6.4)	low	411	6
	956					black	259	F	1368	Yes	1110	Yes	1301		med	1859	
	1					hispanic	145								high	601	
	1915					other	101										
15	0	122.0 (15.6)	51.7 (12.1)	148.3 (60.8)	63.3 (9.5)	white	439	M	305	No	366	No	0	27.5 (3.4)	low	0	6
	224					black	1	F	138	Yes	77	Yes	443		med	443	
	1					hispanic	0								high	0	
	219					other	3										
16	0	186.0 (46.0)	49.8 (12.1)	134.1 (58.5)	52.3 (12.8)	white	545	M	321	No	553	No	409	27.2 (4.1)	low	0	4
	303					black	7	F	273	Yes	41	Yes	185		med	594	
	1					hispanic	32								high	0	
	291					other	10										
17	0	91.8 (24.7)	48.1 (10.9)	167.5 (98.0)	58.1 (9.7)	white	116	M	120	No	0	No	0	33.1 (6.5)	low	0	12
	107					black	28	F	90	Yes	210	Yes	210		med	210	
	1					hispanic	52								high	0	
	103					other	14										
18	0	119.2 (18.5)	51.5 (11.9)	156.3 (59.5)	57.4 (9.9)	white	113	M	100	No	184	No	113	28.7 (4.6)	low	0	6
	92					black	10	F	84	Yes	0	Yes	71		med	92	
	1					hispanic	0								high	92	
	92					other	61										
19	0	89.2 (16.2)	47.2 (10.4)	142.9 (58.1)	61.3 (9.5)	white	451	M	337	No	261	No	306	31.4 (6.4)	low	0	6
	277					black	55	F	217	Yes	293	Yes	248		med	0	
	1					hispanic	0								high	554	
	277					other	48										

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Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
20	0	122.5 (14.7)	51.3 (12.1)	150.8 (61.3)	63.1 (10.3)	white	408	M	297	No	362	No	0	27.3 (3.5)	low	136	6
	207					black	0	F	113	Yes	48	Yes	410		med	274	
	1					hispanic	0								high	0	
	203					other	2										
21	0	102.1 (24.4)	54.8 (13.1)	127.0 (53.5)	71.2 (4.7)	white	984	M	482	No	812	No	1028	28.6 (4.5)	low	0	6
	515					black	37	F	546	Yes	216	Yes	0		med	1028	
	1					hispanic	0								high	0	
	513					other	7										
22	0	122.5 (14.8)	51.1 (12.3)	147.0 (60.8)	61.1 (10.4)	white	345	M	251	No	308	No	0	27.9 (3.4)	low	118	6
	186					black	2	F	112	Yes	55	Yes	363		med	245	
	1					hispanic	0								high	0	
	177					other	16										
23	0	124.9 (18.0)	54.3 (12.8)	140.6 (58.8)	63.3 (9.8)	white	392	M	263	No	314	No	0	28.5 (4.3)	low	0	6
	209					black	4	F	162	Yes	111	Yes	425		med	425	
	1					hispanic	0								high	0	
	216					other	29										
24	0	93.6 (26.7)	49.8 (12.6)	153.2 (74.4)	62.2 (9.8)	white	465	M	318	No	0	No	0	29.3 (5.1)	low	0	6
	212					black	4	F	317	Yes	635	Yes	635		med	635	
	1					hispanic	55								high	0	
	423					other	111										
25	0	124.5 (16.4)	55.3 (13.9)	139.7 (60.1)	63.2 (10.0)	white	599	M	360	No	436	No	313	28.1 (4.7)	low	0	6
	297					black	2	F	241	Yes	165	Yes	288		med	601	
	1					hispanic	0								high	0	
	304					other	0										
26	0	138.2 (41.2)	49.4 (11.6)	151.1 (64.9)	59.9 (11.7)	white	642	M	415	No	529	No	213	29.4 (6.2)	low	135	8
	356					black	39	F	294	Yes	180	Yes	496		med	394	

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Trial	Trt *n*	Baseline LDL-C Mean (SD)	Baseline HDL-C Mean (SD)	Baseline TG Mean (SD)	Age Mean (SD)	Race		Gender		DM		CHD		BMI Mean (SD)	Statin Potency		Duration
	1					hispanic	13								high	180	
	353					other	15										

Table 3

Posterior Estimates of the Parameters under $\mathcal{M}_3$

	LDL-C				HDL-C				TG			
		Posterior				Posterior				Posterior		
Variable	**Parameter**	**Mean**	**SD**	**95% HPD Interval**	**Parameter**	**Mean**	**SD**	**95% HPD Interval**	**Parameter**	**Mean**	**SD**	**95% HPD Interval**
bl_ldlc	β_{11}	−0.079	0.006	(−0.092, −0.067)	β_{21}	−0.001	0.003	(−0.006, 0.005)	β_{31}	-3×10^{-4}	0.003	(−0.006, 0.006)
bl_hdlc	β_{12}	−0.006	0.003	(−0.012, 0.001)	β_{22}	−0.069	0.010	(−0.090, −0.052)	β_{32}	3×10^{-4}	0.003	(−0.005, 0.005)
bl_trig	β_{13}	0.013	0.003	(0.006, 0.019)	β_{23}	0.031	0.005	(0.022, 0.041)	β_{33}	−0.119	0.006	(−0.131, −0.107)
BMI	β_{14}	0.005	0.003	(−0.001, 0.010)	β_{24}	−0.020	0.004	(−0.028, −0.014)	β_{34}	0.018	0.003	(0.013, 0.023)
age	β_{15}	−0.051	0.005	(−0.060, −0.043)	β_{25}	0.016	0.003	(0.010, 0.022)	β_{35}	−0.010	0.002	(−0.015, −0.006)
duration	β_{16}	0.007	0.095	(−0.195, 0.182)	β_{26}	−0.004	0.085	(−0.175, 0.160)	β_{36}	0.017	0.040	(−0.061, 0.096)
Female	β_{17}	0.005	0.003	(−0.001, 0.011)	β_{27}	0.013	0.003	(0.008, 0.019)	β_{37}	0.014	0.002	(0.009, 0.018)
DM	β_{18}	−0.039	0.004	(−0.047, −0.031)	β_{28}	−0.015	0.003	(−0.022, −0.009)	β_{38}	0.001	0.003	(−0.005, 0.006)
CHD	β_{19}	0.004	0.004	(−0.003, 0.011)	β_{29}	−0.008	0.003	(−0.014, −0.003)	β_{39}	0.003	0.003	(−0.002, 0.009)
potency2	$\beta_{1,10}$	−0.066	0.006	(−0.079, −0.054)	$\beta_{2,10}$	0.006	0.003	(−0.000, 0.013)	$\beta_{3,10}$	−0.016	0.004	(−0.023, −0.009)
potency3	$\beta_{1,11}$	−0.146	0.010	(−0.167, −0.127)	$\beta_{2,11}$	0.001	0.004	(−0.006, 0.007)	$\beta_{3,11}$	−0.044	0.004	(−0.052, −0.036)
Black	$\beta_{1,12}$	0.020	0.003	(0.014, 0.027)	$\beta_{2,12}$	−0.009	0.003	(−0.014, −0.004)	$\beta_{3,12}$	−0.010	0.002	(−0.015, −0.006)
Hispanic	$\beta_{1,13}$	0.006	0.003	(0.000, 0.011)	$\beta_{2,13}$	−0.007	0.002	(−0.011, −0.002)	$\beta_{3,13}$	0.006	0.002	(0.001, 0.010)
Other	$\beta_{1,14}$	−0.004	0.003	(−0.010, 0.001)	$\beta_{2,14}$	−0.003	0.002	(−0.007, 0.001)	$\beta_{3,14}$	−0.001	0.002	(−0.005, 0.003)
Means of random effects	γ_{10}	5.297	0.257	(4.791, 5.794)	γ_{20}	7.767	0.632	(6.632, 9.077)	γ_{30}	4.570	0.128	(4.319, 4.825)
	γ_{11}	−0.403	0.036	(−0.476, −0.335)	γ_{21}	0.050	0.017	(0.018, 0.084)	γ_{31}	−0.090	0.017	(−0.125, −0.059)
	γ_{12}	6.256	0.334	(5.603, 6.913)	γ_{22}	7.486	0.605	(6.364, 8.699)	γ_{32}	4.617	0.138	(4.345, 4.890)
	γ_{13}	−0.467	0.057	(−0.583, −0.358)	γ_{23}	0.023	0.015	(−0.005, 0.053)	γ_{33}	−0.095	0.018	(−0.130, −0.059)
Variance of random effects	V_{100}	0.300	0.163	(0.093, 0.615)	V_{200}	0.193	0.114	(0.050, 0.408)	V_{300}	0.029	0.017	(0.008, 0.061)
	V_{101}	−0.019	0.019	(−0.060, 0.013)	V_{201}	−0.004	0.009	(−0.022, 0.013)	V_{301}	−0.002	0.004	(−0.011, 0.005)
	V_{111}	0.008	0.004	(0.002, 0.015)	V_{211}	0.003	0.002	(0.001, 0.006)	V_{311}	0.003	0.002	(0.001, 0.006)
	V_{122}	0.751	0.391	(0.229, 1.480)	V_{222}	0.252	0.149	(0.063, 0.535)	V_{322}	0.079	0.043	(0.023, 0.162)
	V_{123}	−0.104	0.066	(−0.233, −0.012)	V_{223}	0.004	0.009	(−0.013, 0.023)	V_{323}	−0.005	0.007	(−0.019, 0.006)

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	LDL-C				HDL-C				TG			
		Posterior				Posterior				Posterior		
Variable	**Parameter**	**Mean**	**SD**	**95% HPD Interval**	**Parameter**	**Mean**	**SD**	**95% HPD Interval**	**Parameter**	**Mean**	**SD**	**95% HPD Interval**
	V_{133}	0.029	0.016	(0.009, 0.058)	V_{233}	0.002	0.001	(0.001, 0.004)	V_{333}	0.003	0.002	(0.001, 0.006)
Transform. parameters	λ_1	0.127	0.025	(0.078, 0.178)	λ_2	0.198	0.034	(0.132, 0.267)	λ_3	0.012	0.022	(−0.032, 0.054)
	τ_1	0.101	0.015	(0.074, 0.131)	τ_2	0.094	0.014	(0.069, 0.122)	τ_3	0.094	0.014	(0.070, 0.122)

Table 4

Posterior estimates of Σ (Covariance Matrix and Correlations) under $\mathcal{M}_3$

Parameter	Mean	SD	95% HPD interval
Σ_{11}	0.152	0.020	(0.115, 0.191)
Σ_{22}	0.079	0.023	(0.043, 0.126)
Σ_{33}	0.092	0.009	(0.075, 0.110)
Σ_{12}	0.008	0.002	(0.006, 0.011)
Σ_{13}	0.021	0.002	(0.017, 0.025)
Σ_{23}	−0.021	0.003	(−0.028, −0.016)
ρ_{12}	0.077	0.007	(0.064, 0.091)
ρ_{13}	0.177	0.007	(0.164, 0.190)
ρ_{23}	−0.253	0.006	(−0.265, −0.240)

Table 5

Posterior Estimates of the Parameters under $\mathcal{M}_1$

	LDL-C				HDL-C				TG			
		Posterior				Posterior				Posterior		
Variable	Parameter	Mean	SD	95% HPD Interval	Parameter	Mean	SD	95% HPD Interval	Parameter	Mean	SD	95% HPD Interval
bl_ldlc	β_{11}	−3.278	0.156	(−3.594, −2.988)	β_{21}	−0.012	0.112	(−0.226, 0.214)	β_{31}	−0.238	0.267	(−0.766, 0.278)
bl_hdlc	β_{12}	−0.274	0.131	(−0.531, −0.021)	β_{22}	−2.861	0.096	(−3.050, −2.672)	β_{32}	0.145	0.232	(−0.302, 0.613)
bl_trig	β_{13}	0.544	0.125	(0.291, 0.783)	β_{23}	1.307	0.091	(1.128, 1.484)	β_{33}	−8.884	0.221	(−9.313, −8.456)
BMI	β_{14}	0.035	0.121	(−0.202, 0.272)	β_{24}	−0.880	0.088	(−1.053, −0.707)	β_{34}	1.149	0.212	(0.740, 1.569)
age	β_{15}	−1.905	0.121	(−2.149, −1.674)	β_{25}	0.610	0.088	(0.437, 0.781)	β_{35}	−1.282	0.215	(−1.692, −0.858)
duration	β_{16}	1.210	0.699	(−0.177, 2.601)	β_{26}	0.115	0.144	(−0.162, 0.400)	β_{36}	0.008	0.472	(−0.897, 0.977)
Female	β_{17}	0.375	0.120	(0.134, 0.604)	β_{27}	0.565	0.088	(0.391, 0.736)	β_{37}	0.713	0.216	(0.289, 1.128)
DM	β_{18}	−1.295	0.138	(−1.560, −1.018)	β_{28}	−0.653	0.098	(−0.843, −0.461)	β_{38}	0.355	0.236	(−0.114, 0.813)
CHD	β_{19}	0.060	0.144	(−0.224, 0.347)	β_{29}	−0.333	0.101	(−0.532, −0.139)	β_{39}	0.528	0.251	(0.040, 1.022)
potency2	$\beta_{1,10}$	−2.168	0.190	(−2.545, −1.805)	$\beta_{2,10}$	0.211	0.130	(−0.045, 0.462)	$\beta_{3,10}$	−1.372	0.320	(−2.001, −0.741)
potency3	$\beta_{1,11}$	−4.647	0.197	(−5.036, −4.273)	$\beta_{2,11}$	−0.053	0.134	(−0.322, 0.202)	$\beta_{3,11}$	−3.289	0.336	(−3.951, −2.626)
Black	$\beta_{1,12}$	0.810	0.122	(0.572, 1.046)	$\beta_{2,12}$	−0.418	0.087	(−0.585, −0.244)	$\beta_{3,12}$	−0.594	0.209	(−1.008, −0.184)
Hispanic	$\beta_{1,13}$	0.223	0.111	(0.005, 0.441)	$\beta_{2,13}$	−0.275	0.081	(−0.437, −0.118)	$\beta_{3,13}$	0.513	0.196	(0.147, 0.915)
Other	$\beta_{1,14}$	−0.039	0.114	(−0.254, 0.191)	$\beta_{2,14}$	−0.120	0.083	(−0.281, 0.043)	$\beta_{3,14}$	−0.020	0.201	(−0.409, 0.380)
Means of random effects	γ_{10}	61.549	1.600	(58.387, 64.714)	γ_{20}	104.988	0.512	(103.971, 106.008)	γ_{30}	84.265	1.118	(82.160, 86.572)
	γ_{11}	−13.121	0.851	(−14.793, −11.442)	γ_{21}	2.192	0.465	(1.290, 3.122)	γ_{31}	−6.169	0.868	(−7.922, −4.483)
	γ_{12}	90.267	1.744	(86.627, 93.601)	γ_{22}	101.481	0.418	(100.674, 102.333)	γ_{32}	99.679	1.055	(97.592, 101.769)
	γ_{13}	−19.176	1.622	(−22.341, −15.858)	γ_{23}	1.082	0.303	(0.480, 1.674)	γ_{33}	−9.061	0.893	(−10.787, −7.276)
Variance of random effects	V_{100}	28.527	14.853	(8.619, 56.702)	V_{200}	2.734	1.538	(0.656, 5.607)	V_{300}	10.465	7.636	(0.347, 24.659)
	V_{101}	−10.978	7.055	(−24.707, −0.483)	V_{201}	−2.293	1.309	(−4.798, −0.528)	V_{301}	−6.602	5.864	(−18.385, 1.713)
	V_{111}	7.785	4.315	(2.039, 15.954)	V_{211}	2.003	1.215	(0.373, 4.317)	V_{311}	4.764	4.820	(0.001, 13.712)
	V_{122}	37.821	19.204	(12.180, 73.907)	V_{222}	1.524	1.004	(0.215, 3.441)	V_{322}	9.713	6.266	(1.725, 21.593)
	V_{123}	−27.313	16.095	(−59.629, −5.910)	V_{223}	−0.568	0.577	(−1.712, 0.218)	V_{323}	−6.504	4.923	(−15.807, 0.031)

Variable	LDL-C				HDL-C				TG			
		Posterior				Posterior				Posterior		
	Parameter	Mean	SD	95% HPD Interval	Parameter	Mean	SD	95% HPD Interval	Parameter	Mean	SD	95% HPD Interval
	V_{133}	32.349	17.364	(9.267, 65.652)	V_{233}	0.292	0.358	(0.001, 0.945)	V_{333}	4.759	4.326	(0.002, 12.709)

Table 6

Posterior estimates of Σ (Covariance Matrix and Correlations) under $\mathcal{M}_1$

Parameter	Mean	SD	95% HPD interval
Σ_{11}	251.085	2.444	(246.164, 255.747)
Σ_{22}	134.641	1.310	(132.017, 137.155)
Σ_{33}	792.167	7.621	(777.256, 807.082)
Σ_{12}	13.299	1.268	(10.875, 15.851)
Σ_{13}	72.670	3.114	(66.372, 78.542)
Σ_{23}	−73.190	2.302	(−77.642, −68.650)
ρ_{12}	0.072	0.007	(0.059, 0.086)
ρ_{13}	0.163	0.007	(0.150, 0.176)
ρ_{23}	−0.224	0.007	(−0.237, −0.211)