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BAYESIAN MODELING AND INFERENCE FOR META-DATA WITH APPLICATIONS IN EFFICACY EVALUATION OF AN ALLERGIC RHINITIS DRUG

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Abstract

Allergic rhinitis is an allergic inflammation of the nasal membranes. The symptoms include disorders in nose and eyes. Studies have been carried out on safety and efficacy evaluation of triamcinolone acetonide aqueous nasal spray. To combine the results from different studies, we propose random-coefficient regression models. The properties of the proposed models are examined. The models are compared via the deviance information criterion (DIC), and Bayesian computations are carried out via MCMC sampling. A set of meta-data from nine clinical trials is analyzed in detail via the proposed methodology.

Keywords

Gibbs sampling; Meta-analytic regression model; Posterior; Profile likelihood; Random coefficients

1. INTRODUCTION

Often called “hay fever,” allergic rhinitis is the sixth most common form of chronic illness in the United States, affecting 10–30% of adults and up to 40% of children (Wallace et al., 2008). Allergic rhinitis is an aberration of the immune response in which the body reacts in response to an otherwise harmless airborne substance categorized as an allergen (or antigen). Common aeroallergens implicated in allergic rhinitis include dust, mold, and pollen. The disease is characterized by sneezing, congestion, clear rhinorrhea, and nasal or palatal itching. The disease may also coexist with allergic conjunctivitis (characterized by itchy, watery eyes that may also be red or swollen). The severity of allergic rhinitis ranges from mild and intermittent to seriously debilitating. Allergic rhinitis may be seasonal (triggered by common seasonal allergens), perennial (triggered by common allergens that are year-round), or may occur sporadically after specific exposures. The goal of pharmacotherapy is to relieve symptoms. Interventions range from avoidance of allergens and medications to immunotherapy (Wallace et al., 2008).

Gender differences in the prevalence of allergic disease have been reported and appear to be age related. In a birth cohort study of 1218 children in the United Kingdom who were examined at 4 years of age for the presence of allergic diseases (asthma, rhinitis, or eczema), Arshad et al. (2001) reported that boys were sensitive to a greater number of allergens. A series of surveys conducted in northeastern England involving children aged 6 to 7 years and 13 to 14 years found that in prepubertal children the prevalence of rhinitis was higher in males than in females (Shamssain and Shamsian, 1999), while in adolescents the prevalence of allergic rhinitis was relatively higher in girls than in boys (Shamssain and Shamsian, 2001). Although differences in prevalence and pathophysiology have been demonstrated between males and females, it is not known whether or not they translate into differences in symptom severity and treatment efficacy. One of the objectives of this paper is to develop a meta-analytic regression model using the data from nine randomized, double-blind, parallel-group, and controlled clinical studies. Another objective is to understand whether there is gender difference in response to treatment with triamcinolone acetonide aqueous nasal spray (TAA AQ), an intranasal glucocorticoid indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis.

There is a rich literature on statistical methods using random effects models for meta-analysis. Nowadays, random effects modeling has become a standard approach for meta-analysis. See, for example, Whitehead and Whitehead (1991), Hardy and Thompson (1996), Higgs and Whitehead (1996), Biggerstaff and Tweedie (1997), Aitkin (1999), Normand (1999), Brockwell and Gordon (2001), Burr and Doss (2005), and Sutton and Higgins (2008). In meta-analyses using random effects models for normally distributed data, it has been quite common in the literature to assume that the variance of the error term for an aggregate response is fixed to a known value and is taken as the estimated variance of the aggregate response (see, Whitehead, 2002). In this paper, we assume that the variance is unknown and develop an additional model for the unknown variance via the distribution of the estimated variance of the aggregate response.

The remainder of the paper is organized as follows. Section 2 gives a brief description of the TAA AQ data. Section 3 provides a full development of two multidimensional random coefficients regression models, the properties of the proposed models, and the connection between these two models. In section 4, we discuss the priors and posteriors for Bayesian inference, present the computational development, and develop deviance information criteria (DIC) for model comparison. Section 5 presents a detailed analysis of the TAA AQ data. We conclude the paper with some discussion and extension in section 6.

2. THE TAA AQ DATA

TAA AQ is an intranasal glucocorticoid indicated for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis. We searched its original New Drug Application (NDA) submitted to the US Food and Drug Administration and identified all controlled clinical studies that were reported in the original NDA for inclusion in this meta-analysis. There were nine controlled studies that were completed between 1992 and 1994 to evaluate the safety and efficacy of TAA AQ, compared with placebo. Although the individual studies varied somewhat in terms of allergy season, patient age range, and disease

state, all nine studies had common design features: randomized, double-blind, parallel-group. All of them included placebo and TAA AQ 220 µg once daily treatment arms, with some studies including TAA AQ at various daily doses between 0 (placebo) and 220 µg once daily in the morning. All study participants were required to be at least 12 years of age and to have either seasonal or perennial allergic rhinitis.

Each of the trials consisted of two phases, a baseline phase of 4 days, followed by a double-blind efficacy phases of 2 to 4 weeks. Daily symptom diary was completed by patients each evening before bedtime, reflecting the previous 24 hours. The primary allergy symptom scores for nasal stuffiness, nasal discharge, and sneezing were collected in all protocols. These daily diary symptom scores were rated by the patients on a 4-point scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Each study assessed efficacy using change from baseline in nasal index score (NIS, the sum of nasal stuffiness, nasal discharge, and sneezing symptom scores). For a patient, the mean change from baseline in NIS was defined as the average over the daily change for days 1 through 14 for a 2-week study, days 1 through 21 for a 3-week study, and days 1 through 28 for a 4-week study. Baseline was defined as the average for the last 4 days of efficacy readings prior to dosing.

The NIS changes from baseline from the nine studies are summarized by TAA AQ dose level, gender, and study in Fig. 1.

3. META-ANALYTIC RANDOM COEFFICIENTS REGRESSION MODELS

3.1. The Models

In contrast to using treatment difference as the analysis variable in most meta-analysis literature, this paper uses the mean changes from baseline within each dose level. Suppose we consider K randomized trials, where each trial has m_k dose levels. Let y_{jk} denote the mean changes from baseline in nasal index score from n_{jk} individual subjects with standard error se_{jk} , and let $w_{jk} = 1/se_{jk}^2$ be the observed precision of y_{jk} . Also, let $dose_{jk}$ denote the dose level in micrograms. The possible values of $dose_{jk}$ are 0, denoting “placebo,” 275 µg, 55 µg, 110 µg, and 220 µg. In the proposed models presented next, we use the natural logarithm transformation of $(dose_{jk} + 1)$, that is, $\log(dose_{jk} + 1)$, instead of $dose_{jk}$. We further denote $gender_{jk} = 1$ for male and 0 for female. Write $S_{jk}^2 = n_{jk}w_{jk}^{-1}$ and assume y_{jk} and S_{jk}^2 are independent for $j = 1, 2, \dots, m_k$ and $k = 1, 2, \dots, K$.

We propose two random coefficient regression models to fit the meta-data just described. The first model assumes

$$y_{jk} = \mathbf{x}_{jk}'\boldsymbol{\beta} + \mathbf{z}_{jk}'\boldsymbol{\gamma}_k + \epsilon_{jk}, \quad \epsilon_{jk} \sim N(0, w_{jk}^{-1}) \quad (1)$$

where $\mathbf{x}_{jk}$ is a p -dimensional vector of covariates, $\mathbf{z}_{jk}$ is a q -dimensional vector of covariates, $\boldsymbol{\beta}$ is a p -dimensional vector of fixed regression coefficients corresponding to $\mathbf{x}_{jk}$, and $\boldsymbol{\gamma}_k$ is a

q -dimensional vector of random regression coefficients corresponding to z_{jk} . In Eq. (1), we further assume that

$$\boldsymbol{\gamma}_k \sim N(\mathbf{0}, \Omega) \quad (2)$$

where Ω is a $q \times q$ variance-covariance matrix. The random coefficients $\boldsymbol{\gamma}_k$, which are assumed to be independent of $\boldsymbol{\epsilon}_{jk}$, capture heterogeneity across K trials. We consider different forms of $\mathbf{x}_{jk}$ and $\mathbf{z}_{jk}$ in terms of functions of $\log(\text{dose}_{jk} + 1)$ and gender_{jk} . If we take $\mathbf{x}_{jk} = (1, \log(\text{dose}_{jk} + 1), \text{gender}_{jk})'$, and $\mathbf{z}_{jk} = (1, \log(\text{dose}_{jk} + 1))'$, then model (1) is called a main effects model. Other forms include, for example, $\mathbf{x}_{jk} = (1, \log(\text{dose}_{jk} + 1), \text{gender}_{jk}, \log(\text{dose}_{jk} + 1)\text{gender}_{jk})'$, and $\mathbf{z}_{jk} = (1, \log(\text{dose}_{jk} + 1), \log(\text{dose}_{jk} + 1)\text{gender}_{jk})'$ (interaction model); and $\mathbf{x}_{jk} = (1, \log(\text{dose}_{jk} + 1), \text{gender}_{jk}, \log(\text{dose}_{jk} + 1)\text{gender}_{jk}, (\log(\text{dose}_{jk} + 1))^2, (\log(\text{dose}_{jk} + 1))^2\text{gender}_{jk})'$, and $\mathbf{z}_{jk} = (1, \log(\text{dose}_{jk} + 1), \log(\text{dose}_{jk} + 1)\text{gender}_{jk}, (\log(\text{dose}_{jk} + 1))^2, (\log(\text{dose}_{jk} + 1))^2\text{gender}_{jk})'$ (quadratic model). In section 5, we use the Bayesian deviance information criterion (DIC) of Spiegelhalter et al. (2002) to compare various forms of $\mathbf{x}_{jk}$ and $\mathbf{z}_{jk}$.

The second model we propose is to relax the assumption of known variance in Eq. (1). The general form of our second model is given by

$$y_{jk} = \mathbf{x}'_{jk}\boldsymbol{\beta} + \mathbf{z}'_{jk}\boldsymbol{\gamma}_k + \epsilon_{jk}, \quad \epsilon_{jk} \sim N\left(0, \frac{\sigma_{jk}^2}{n_{jk}}\right) \quad (3)$$

and

$$(n_{jk} - 1)S_{jk}^2 \sim \sigma_{jk}^2 \chi_{n_{jk} - 1}^2 \quad (4)$$

where $\chi_{n_{jk} - 1}^2$ denotes the χ^2 -distribution with $(n_{jk} - 1)$ degrees of freedom. In Eq. (3) Eq. (2) is assumed for $\boldsymbol{\gamma}_k$. When the individual subject-level data $y_{ijk} \sim i.i.d. \cdot N(\mu_{jk}, \sigma_{jk}^2)$ for $i = 1, 2, \dots, n_{jk}$, then (y_{jk}, S_{jk}^2) are independent and sufficient statistics for μ_{jk} and σ_{jk}^2 . Thus, the model given in Eqs. (3) and (4) based on the dose-level meta-data provides exactly the same information about μ_{jk} and σ_{jk}^2 as the model based on the individual subject-level data.

In our first model (1), the variance of the meta data response y_{jk} is fixed to be w_{jk}^{-1} . We notice that this approach has been commonly used to model meta-data with covariates (Whitehead, 2002). As discussed earlier, our second model uses the sufficient statistics, which prevents the loss of information for fitting the metadata. Thus, our second model can be used as a benchmark model for assessing information loss when model (1) is used. In addition, under both models, we consider multidimensional random coefficients and, hence, both models are new in this sense.

3.2. The Likelihood Functions and Properties

In this subsection, we present the likelihood functions under both models given in the previous subsection and discuss a connection between these two likelihood functions. Let

$D_{obs} = \{(y_{jk}, n_{jk}, se_{jk}, n_{jk}, x_{jk}, z_{jk}), j = 1, 2, \dots, m_k, k = 1, 2, \dots, K\}$ denote the observed meta data and also let $D_c = \{(y_{jk}, n_{jk}, se_{jk}, n_{jk}, x_{jk}, z_{jk}, \gamma_{jk}), j = 1, 2, \dots, m_k, k = 1, 2, \dots, K\}$ denote the complete data. The complete data likelihood function under model (1) is given by

$$L_{1c}(\beta, \Omega \mid D_c) = \prod_{k=1}^K \left(\prod_{j=1}^{m_k} \left[\frac{w_{jk}^{1/2}}{\sqrt{2\pi}} \exp \left\{ -\frac{w_{jk}}{2} (y_{jk} - \mu_{jk})^2 \right\} \right] \times \frac{|\Omega|^{-1/2}}{(2\pi)^{q/2}} \exp \left\{ -\frac{1}{2} \gamma_k' \Omega^{-1} \gamma_k \right\} \right) \quad (5)$$

where

$$\mu_{jk} = \mathbf{x}_{jk}' \beta + \mathbf{z}_{jk}' \gamma_k \quad (6)$$

Let $\sigma^2 = (\sigma_{jk}^2, j = 1, 2, \dots, m_k, k = 1, 2, \dots, K)$. The complete data likelihood function under the model defined in Eqs. (3) and (4) is given by

$$\begin{aligned} L_{2c}(\beta, \sigma^2, \Omega \mid D_c) &= \prod_{k=1}^K \left(\prod_{j=1}^{m_k} \left[\frac{n_{jk}^{1/2}}{\sqrt{2\pi\sigma_{jk}^2}} \exp \left\{ -\frac{n_{jk}}{2\sigma_{jk}^2} (y_{jk} - \mu_{jk})^2 \right\} \right. \right. \\ &\quad \left. \left. \times \frac{1}{2^{\frac{n_{jk}-1}{2}} \Gamma\left(\frac{n_{jk}-1}{2}\right)} \left\{ (n_{jk}-1) S_{jk}^2 \right\}^{\frac{n_{jk}-1}{2}-1} \times \left(\frac{1}{\sigma_{jk}^2} \right)^{\frac{n_{jk}-1}{2}} \times \exp \left\{ -\frac{(n_{jk}-1) S_{jk}^2}{2\sigma_{jk}^2} \right\} \right. \right. \\ &\quad \left. \left. \times \frac{|\Omega|^{-1/2}}{(2\pi)^{q/2}} \exp \left\{ -\frac{1}{2} \gamma_k' \Omega^{-1} \gamma_k \right\} \right] \right) \\ &= \prod_{k=1}^K \left(\prod_{j=1}^{m_k} \left[\exp \left\{ -\frac{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk}-1) S_{jk}^2}{2\sigma_{jk}^2} \right\} \times \frac{n_{jk}^{1/2}}{\pi^{1/2} 2^{\frac{n_{jk}}{2}} \Gamma\left(\frac{n_{jk}-1}{2}\right)} \right. \right. \\ &\quad \left. \left. \times \left\{ (n_{jk}-1) S_{jk}^2 \right\}^{\frac{n_{jk}-1}{2}-1} \left(\frac{1}{\sigma_{jk}^2} \right)^{\frac{n_{jk}}{2}} \times \frac{|\Omega|^{-1/2}}{(2\pi)^{q/2}} \exp \left\{ -\frac{1}{2} \gamma_k' \Omega^{-1} \gamma_k \right\} \right] \right) \end{aligned} \quad (7)$$

Thus the logarithm of the complete data likelihood function becomes

$$\begin{aligned} \log L_{2c}(\beta, \sigma^2, \Omega \mid D_c) &= -\frac{1}{2} \sum_{k=1}^K \sum_{j=1}^{m_k} \left[\frac{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk}-1) S_{jk}^2}{\sigma_{jk}^2} + n_{jk} \log \sigma_{jk}^2 \right] \\ &\quad + g(\Omega \mid D_c) \end{aligned}$$

where $g(\Omega|D_c)$ is a function of Ω given the complete data D_c , which is independent of σ_{jk}^2 . Differentiating the logarithm of the complete data likelihood function with respect to σ_{jk}^2 gives

$$\frac{\partial \log L_{2c}(\boldsymbol{\beta}, \sigma^2, \Omega | D_c)}{\partial \sigma_{jk}^2} = \frac{1}{2} \left[\frac{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk} - 1)S_{jk}^2}{\sigma_{jk}^4} - \frac{n_{jk}}{\sigma_{jk}^2} \right]$$

Solving the equation $\frac{\partial \log L_{2c}(\boldsymbol{\beta}, \sigma^2, \Omega | D_c)}{\partial \sigma_{jk}^2} = 0$ yields an estimator of σ_{jk}^2 given by

$$\hat{\sigma}_{jk}^2 = \frac{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk} - 1)S_{jk}^2}{n_{jk}}$$

Plugging $\hat{\sigma}_{jk}^2$ in Eq. (7) results in the profile likelihood function of $(\boldsymbol{\beta}, \Omega)$, which is

$$\begin{aligned} L_{p2c}(\boldsymbol{\beta}, \Omega | D_c) &= \prod_{k=1}^K \left(\prod_{j=1}^{m_k} \exp\left(-\frac{n_{jk}}{2}\right) \frac{n_{jk}^{1/2}}{\pi^{1/2} 2^{\frac{n_{jk}}{2}} \Gamma\left(\frac{n_{jk}-1}{2}\right)} \right. \\ &\times \left\{ (n_{jk} - 1)S_{jk}^2 \right\}^{\frac{n_{jk}-1}{2} - 1} \times \left\{ \frac{n_{jk}}{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk} - 1)S_{jk}^2} \right\}^{\frac{n_{jk}}{2}} \\ &\left. \times \frac{|\Omega|^{-1/2}}{(2\pi)^{q/2}} \exp\left\{-\frac{1}{2} \boldsymbol{r}_k' \Omega^{-1} \boldsymbol{r}_k\right\} \right) \end{aligned} \quad (8)$$

Remark 1.—The complete data profile likelihood function of $(\boldsymbol{\beta}, \Omega)$ essentially matches the one obtained from the multidimensional random coefficients regression model (1) with the error term ϵ_{jk} that follows a scaled Student's t distribution with $n_{jk} - 1$ degrees of freedom and a scale parameter S_{jk}^2/n_{jk} , which is precisely w_{jk}^{-1} —thus, ignoring the constants $L_{p2c}(\boldsymbol{\beta}, \Omega|D_c) \approx L_{1c}(\boldsymbol{\beta}, \Omega|D_c)$ when n_{jk} terms are large. This result implies that the model in Eq. (1) with a fixed variance w_{jk}^{-1} is approximately the same as the model defined by Eqs. (3) and (4) when n_{jk} is relatively large.

4. BAYESIAN POSTERIOR INFERENCE

4.1. Priors and Posteriors

For the two random coefficient regression models discussed in section 3, we specify independent priors for $\boldsymbol{\beta}$, Ω , and σ^2 . Specifically, we take a multivariate normal prior $\mathcal{N}(\mathbf{0}, \Sigma_0)$, where Σ_0 is a $p \times p$ variance-covariance matrix, for $\boldsymbol{\beta}$, and an inverse-Wishart distribution, $\text{Inv-Wishart}_{\nu_0}(\Omega_0^{-1})$, for Ω . We further assume independent inverse gamma priors

Inv-Gamma(a, b) for σ_{jk}^2 . Let $\pi(\boldsymbol{\beta}|\Sigma_0)$, $\pi(\Omega|v_0, \Omega_0)$, and $\pi(\sigma_{jk}^2 | a, b)$ denote these three priors, where Σ_0 , v_0 , Ω_0 , and (a, b) are prespecified. Then, we have

$$\begin{aligned}\pi(\boldsymbol{\beta} | \Sigma_0) &\propto \exp\left\{-\frac{1}{2}\boldsymbol{\beta}'\Sigma_0^{-1}\boldsymbol{\beta}\right\}, \quad \pi(\Omega | v_0, \Omega_0) \\ &\propto |\Omega|^{(v_0+q+1)/2} \exp\left\{-\frac{1}{2}\text{tr}(\Omega_0\Omega^{-1})\right\}\end{aligned}\quad (9)$$

and

$$\pi(\sigma_{jk}^2 | a, b) \propto \frac{1}{(\sigma_{jk}^2)^{a+1}} \exp\left(-\frac{b}{\sigma_{jk}^2}\right) \quad (10)$$

Let $\boldsymbol{\gamma} = (\boldsymbol{\gamma}'_1, \boldsymbol{\gamma}'_2, \dots, \boldsymbol{\gamma}'_K)'$. Given the observed data D_{obs} , the posterior distribution of $(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega)$ under model (1) is given as follows:

$$\pi_1(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega | D_{obs}) \propto L_{1c}(\boldsymbol{\beta}, \Omega | D_c) \pi(\boldsymbol{\beta} | \Sigma_0) \pi(\Omega | v_0, \Omega_0) \quad (11)$$

where the complete data likelihood function $L_{1c}(\boldsymbol{\beta}, \Omega | D_c)$ is defined in Eq. (5). Similarly, the posterior distribution of $(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \boldsymbol{\gamma}, \Omega)$ given D_{obs} under the model defined in Eqs. (3) and (4) is of the form

$$\begin{aligned}\pi_2(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \boldsymbol{\gamma}, \Omega | D_{obs}) &\propto L_{2c}(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \Omega | D_c) \pi(\boldsymbol{\beta} | \Sigma_0) \pi(\Omega | v_0, \Omega_0) \prod_{k=1}^K \prod_{j=1}^{m_k} \pi \\ &(\sigma_{jk}^2 | a, b)\end{aligned}\quad (12)$$

where the complete data likelihood function $L_{2c}(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \Omega | D_c)$ is given in Eq. (7).

Now, we discuss a connection between the two posteriors given in Eqs. (11) and (12). Integrating out the σ_{jk}^2 from Eq. (12) leads to the marginal posterior of $(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega)$, which is given by

$$\begin{aligned}\pi_2(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega | D_{obs}) &= \int \pi_2(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \boldsymbol{\gamma}, \Omega | D_{obs}) d\boldsymbol{\sigma}^2 \\ &\propto \prod_{k=1}^K \left(\prod_{j=1}^{m_k} \left\{ \frac{1}{n_{jk}(y_{jk} - \mu_{jk})^2 + (n_{jk} - 1)S_{jk}^2 + 2b} \right\}^{\frac{n_{jk}}{2} + a} \right. \\ &\times \left. \frac{|\Omega|^{-1/2}}{(2\pi)^{q/2}} \exp\left\{-\frac{1}{2}\boldsymbol{\gamma}'_k \Omega^{-1} \boldsymbol{\gamma}_k\right\} \right) \times \pi(\boldsymbol{\beta} | \Sigma_0) \pi(\Omega | v_0, \Omega_0),\end{aligned}\quad (13)$$

where μ_{jk} is defined in Eq. (6).

Remark 2.—The marginal posterior given in Eq. (13) coincides with the posterior distribution of $(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega)$ from the multidimensional random coefficients regression model (1) with the error term $\boldsymbol{\epsilon}_{jk}$ that follows a scaled Student's t distribution with $n_{jk} + 2a - 1$ degrees

of freedom and a scale parameter $\frac{(n_{jk}-1)S_{jk}^2+2b}{n_{jk}(n_{jk}+2a-1)}$. Thus, if we take a Jeffreys type prior for σ_{jk}^2 , namely, $\pi(\sigma_{jk}^2 | a, b)$ with $a = b = 0$ in Eq. (10), then the term ϵ_{jk} follows a scaled Student's t distribution with $n_{jk} - 1$ degrees of freedom and a scale parameter $\frac{S_{jk}}{n_{jk}}$, which is w_{jk}^{-1} . Thus, when a Jeffreys type prior is specified for σ_{jk}^2 and n_{jk} is relatively large, $\pi_1(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega | D_{obs}) \approx \pi_2(\boldsymbol{\beta}, \boldsymbol{\gamma}, \Omega | D_{obs})$. In this case, model (1) does not lose much information compared to the model given in Eqs. (3) and (4).

4.2. The Posterior Computation

Due to the complexity of the random coefficients regression models for the meta-data, it does not appear possible to obtain an analytic evaluation of the posterior distributions given in Eqs. (11) and (12). Due to the recent advance in Markov chain Monte Carlo sampling (Chen et al., 2000), the Gibbs sampling algorithm is relatively easy to carry out sampling from the posterior distributions (11) and (12). For ease of presentation, we discuss how to sample from the posterior distribution (12), as the computation algorithm for sampling from the posterior distribution (11) is even more straightforward. The Gibbs sampling algorithm requires sampling from the following conditional posterior distributions in turn: (i) $[\boldsymbol{\beta} | \sigma^2, \boldsymbol{\gamma}, D_{obs}]$; (ii) $[\sigma^2 | \boldsymbol{\beta}, \boldsymbol{\gamma}, D_{obs}]$; (iii) $[\boldsymbol{\gamma} | \boldsymbol{\beta}, \sigma^2, \Omega, D_{obs}]$; and (iv) $[\Omega | \boldsymbol{\gamma}, D_{obs}]$. We briefly discuss how to sample from each of the conditional posterior distributions next.

For (i), $[\boldsymbol{\beta} | \sigma^2, \boldsymbol{\gamma}, D_{obs}]$ is a multivariate normal distribution given by

$$\boldsymbol{\beta} | \sigma^2, \boldsymbol{\gamma}, D_{obs} \sim N \left(B^{-1} \sum_{k=1}^K \sum_{j=1}^{m_k} \frac{n_{jk}}{\sigma_{jk}^2} \mathbf{x}_{jk} (y_{jk} - \mathbf{z}_{jk}' \boldsymbol{\gamma}_k), B^{-1} \right)$$

where $B = \sum_{k=1}^K \sum_{j=1}^{m_k} \frac{n_{jk}}{\sigma_{jk}^2} \mathbf{x}_{jk} \mathbf{x}_{jk}' + \Sigma_0^{-1}$. For (ii), given $\boldsymbol{\beta}, \boldsymbol{\gamma}$, and D_{obs} , σ_{jk}^2 terms are conditionally independent and follow the inverse gamma distributions given by

$$\sigma_{jk}^2 | \boldsymbol{\beta}, \boldsymbol{\gamma}, D_{obs} \sim \text{Inv-Gamma}(a_{jk}, b_{jk})$$

where $a_{jk} = \frac{n_{jk}}{2} + a$ and $b_{jk} = \frac{1}{2} \{ n_{jk} (y_{jk} - \mu_{jk})^2 + (n_{jk} - 1) S_{jk}^2 + 2b \}$ for $j = 1, 2, \dots, m_k$ and $k = 1, 2, \dots, K$. For (iii), given $\boldsymbol{\beta}, \sigma^2, \Omega$, and D_{obs} , $\boldsymbol{\gamma}_k$ terms are conditionally independent and follow the normal distributions given by

$$\boldsymbol{\gamma}_k | \boldsymbol{\beta}, \sigma^2, \Omega, D_{obs} \sim N \left(V_k^{-1} \sum_{j=1}^{m_k} \frac{n_{jk}}{\sigma_{jk}^2} \mathbf{z}_{jk} (y_{jk} - \mathbf{x}_{jk}' \boldsymbol{\beta}), V_k^{-1} \right)$$

where $V_k = \Omega^{-1} + \sum_{j=1}^{m_k} \frac{n_{jk}}{\sigma_{jk}^2} \mathbf{z}_{jk} \mathbf{z}_{jk}'$ for $k = 1, 2, \dots, K$. Finally, for (iv), we have

$$\Omega \mid \gamma, D_{obs} \sim \text{Inv-Wishart}_{K+1} \left(\Omega_0 + \sum_{k=1}^K \gamma_k \gamma_k' \right)^{-1}$$

Since all of the conditional posteriors above are standard distributions, sampling for these parameters are straightforward.

4.3. The Deviance Information Criterion (DIC)

To carry out Bayesian model comparisons, we use the deviance information criterion (DIC) developed by Spiegelhalter et al. (2002). Due to the nature of random coefficients regression models, we first derive the observed data likelihood functions for both models given in section 3. Let $\mathbf{y}_k = (y_{1k}, y_{2k}, \dots, y_{m_k, k})'$, $\mathbf{X}_k = (\mathbf{x}_{1k}, \mathbf{x}_{2k}, \dots, \mathbf{x}_{m_k, k})'$, and $\mathbf{Z}_k = (\mathbf{z}_{1k}, \mathbf{z}_{2k}, \dots, \mathbf{z}_{m_k, k})'$. Then, $\mathbf{y}_k$ is an m_k -dimensional vector, $\mathbf{X}_k$ is an $m_k \times p$ design matrix of covariates for fixed effects, and $\mathbf{Z}_k$ is an $m_k \times q$ design matrix of covariates for random coefficients. Also let $\mathbf{W}_k = \text{diag}(w_{1k}, w_{2k}, \dots, w_{m_k, k})$ and $\Sigma_k = \text{diag}(\sigma_{1k}^2/n_{1k}, \sigma_{2k}^2/n_{2k}, \dots, \sigma_{m_k, k}^2/n_{m_k, k})$. After some algebra, the observed data likelihood function under model (1) is given by

$$L_{1o}(\boldsymbol{\beta}, \Omega \mid D_{obs}) = \prod_{k=1}^K \frac{|\mathbf{W}_k^{-1} + \mathbf{Z}_k \Omega \mathbf{Z}_k'|^{-\frac{1}{2}}}{(2\pi)^{m_k/2}} \exp \left\{ -\frac{1}{2} (\mathbf{y}_k - \mathbf{X}_k \boldsymbol{\beta})' (\mathbf{W}_k^{-1} + \mathbf{Z}_k \Omega \mathbf{Z}_k')^{-1} (\mathbf{y}_k - \mathbf{X}_k \boldsymbol{\beta}) \right\} \quad (14)$$

In order to define a deviance function for our second model defined by Eqs. (3) and (4), which is comparable to $L_{1o}(\boldsymbol{\beta}, \Omega \mid D_{obs})$, we define the observed data likelihood function only for the response variables $\mathbf{y}_k$ terms based on Eq. (3). Thus, after integrating out the random coefficients γ_k , the observed data likelihood function of the $\mathbf{y}_k$ terms for model (3) is given by

$$L_{2o}(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \Omega \mid D_{obs}) = \prod_{k=1}^K \frac{|\Sigma_k + \mathbf{Z}_k \Omega \mathbf{Z}_k'|^{-\frac{1}{2}}}{(2\pi)^{m_k/2}} \exp \left\{ -\frac{1}{2} (\mathbf{y}_k - \mathbf{X}_k \boldsymbol{\beta})' (\Sigma_k + \mathbf{Z}_k \Omega \mathbf{Z}_k')^{-1} (\mathbf{y}_k - \mathbf{X}_k \boldsymbol{\beta}) \right\} \quad (15)$$

Let $\boldsymbol{\theta} = (\boldsymbol{\beta}, \Omega)$ for model (1) or $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \Omega)$ for Model (3). We define the deviance function as follows:

$$D(\boldsymbol{\theta}) = -2 \log L_{1o}(\boldsymbol{\beta}, \Omega \mid D_{obs}) \text{ or } D(\boldsymbol{\theta}) = -2 \log L_{2o}(\boldsymbol{\beta}, \boldsymbol{\sigma}^2, \Omega \mid D_{obs}) \quad (16)$$

According to Spiegelhalter et al. (2002), the DIC is given by

$$\text{DIC} = D(\bar{\boldsymbol{\theta}}) + 2p_D \quad (17)$$

where $p_D = \overline{D(\theta)} - D(\bar{\theta})$, $\overline{D(\theta)} = E[D(\theta) | D_{obs}]$ (the posterior mean of $D(\theta)$), and $\bar{\theta} = E[\theta | D_{obs}]$ (the posterior mean of θ). In DIC defined by Eq. (17), the first term measures the goodness-of-fit, and p_D is the effective number of model parameters. The DIC in Eq. (17) is a Bayesian measure of fit or adequacy with $2p_D$ being the respective dimensional penalty term. The smaller the DIC value, the better the model fits the data. Note that it is important to integrate out random coefficients γ_k in the deviance calculation as this yields a more appropriate dimensional penalty term $2p_D$. In the DIC calculation for our second model, we may view Eq. (10) as an initial prior for σ_{jk}^2 and consider (n_{jk}, S_{jk}^2) in Eq. (4) as the “historical data.” Combining Eqs. (10) and (4) gives a new “prior” for σ_{jk}^2 , which is given by

$$\pi(\sigma_{jk}^2 | n_{jk}, S_{jk}^2, a, b) \propto \frac{1}{(\sigma_{jk}^2)^{\frac{n_{jk}-1}{2} + a + 1}} \exp\left[-\frac{(n_{jk}-1)S_{jk}^2 + 2b}{2\sigma_{jk}^2}\right] \quad (18)$$

Notice that the new “prior” for σ_{jk}^2 is quite informative. We empirically observe that DIC does not penalize the parameters with informative priors in the same way as it penalizes the parameters with noninformative priors. The penalty for parameters with informative priors is indeed much less than those parameters with noninformative priors. This intuitively makes sense as when the priors are very informative, the parameters are nearly fixed to certain known values.

5. ANALYSIS OF THE TAA AQ DATA

In this section, we present a detailed analysis of the TAA AQ data. In our analysis, we specified $N(\mathbf{0}, 1000I_p)$ for β and improper Inv-Wishart $_{v_0}(\Omega_0^{-1})$ with $v_0 = q - 1$ and $\Omega_0 = 0.01I_q$ for Ω , where I_p and I_q are the $p \times p$ and $q \times q$ identity matrices. In addition, a Jeffreys type prior, that is, $a = b = 0$ in Eq. (10), was specified for σ_{jk}^2 . All priors were relatively noninformative so that our analyses were driven by the data. In all of the computations, we standardized all covariates for numerical stability.

Table 1 shows the DIC values for various forms of $\mathbf{x}_{jk}$ and $\mathbf{z}_{jk}$ under both the first model (1) and the second model defined by Eqs. (3) and (4). In Table 1, Covariates model 1 (the main effects model) denotes $\mathbf{x}'_{jk}\beta = \beta_0 + \beta_1 \log(\text{dose}_{jk} + 1) + \beta_2 \text{gender}_{jk}$ and

$\mathbf{z}'_{jk}\gamma_k = \gamma_{k0} + \gamma_{k1} \log(\text{dose}_{jk} + 1)$; and Covariates model 2 is

$\mathbf{x}'_{jk}\beta = \beta_0 + \beta_1 \log(\text{dose}_{jk} + 1) + \beta_2 \text{gender}_{jk}$ and $\mathbf{z}'_{jk}\gamma_k = \gamma_{k0}$. Thus, only a single random intercept is included in Covariates model 2. We observed from Table 1 that (i) given the same $\mathbf{x}_{jk}$, the random intercept models had larger DICs than those $\mathbf{z}_{jk}$ models, including random slopes; (ii) the models with dose and gender interactions did not improve the goodness-of-fit much over those without the interactions; (iii) the main effects model, namely, Covariates Model 1, had the smallest DIC value among the six covariates models we considered; and (iv) the DIC values between model (1) and model (3) and (4) were fairly close except for those with a random intercept only. We also observed that the values of p_D

under model (1) were close to those under model (3) and (4). For example, for Covariates model 1, $p_D = 6.18$ under model (1) while $p_D = 6.21$ under model (3) and (4); for Covariates model 2, $p_D = 3.64$ under model (1) while $p_D = 4.07$ under model (3) and (4). We used SAS Procedure NLMIXED to compute the maximum likelihood estimates of the parameters under model (1). The optimization failed to converge when $q > 2$. However, for Covariates Models 1 and 2, the optimizations did converge. The AIC values were 54.0 for Covariates Model 1 and 64.2 for Covariates Model 2, which includes only a single random intercept in $z'_{jk}\gamma_k$. These AIC values were close to the corresponding DIC values under model (1). These results further confirm that a single random intercept was not sufficient to capture heterogeneity among different doses within trials.

Table 2 shows the posterior estimates, the maximum likelihood estimates (MLEs) for model (1), and the profile maximum likelihood estimates (PMLEs) for model (3) and (4) of β and Ω under Covariates model 1 in Table 1. Both MLEs and PMLEs were computed using SAS Procedure NLMIXED. From Table 2, we observed that (i) the posterior estimates of β were close between model (1) and model (3) and (4); (ii) the MLEs of β were very similar to the PMLEs of β ; (iii) for model (1), the posterior estimates of β were close to the MLEs of β ; and (iv) for model (3) and (4), the posterior estimates of β were close to the PMLEs of β . Under both models, the posterior estimates, the MLEs, and PMLEs indicated that the dose effect was significant (the 95% highest posterior density (HPD) intervals were $(-0.817, -0.449)$ and $(-0.825, -0.458)$; and the p -values were less than 0.001) and that the gender effect was not significant (the 95% HPD intervals were $(-0.088, 0.077)$ and $(-0.089, 0.081)$; and the p -values were 0.890 and 0.897). For Covariates model 3, the posterior means, posterior standard deviations (SDs), and 95% HPD intervals of the regression coefficients were $-0.048, 0.064$, and $(-0.171, 0.077)$ for gender, and $0.100, 0.097$, and $(-0.090, 0.292)$ for $\log(\text{dose} + 1)$ and gender interaction under model (1). The corresponding posterior estimates under model (3) and (4) were similar. These results further show that there was no significant difference in mean change in Nasal Index Score from baseline between female and male.

From both Tables 1 and 2, we empirically observed that model (1), in which the error variance was fixed to the standard error of the sample mean, yielded similar parameter estimates and slightly larger DICs compared to model (3) and (4) based on sufficient statistics. As discussed in Remarks 1 and 2, when n_{jk} terms are large, both models are approximately the same. For the TAA AQ data, the median value of the sample sizes n_{jk} terms was 38 with an inter-quartile range of (30, 48). Except for two small trials with sample sizes of 4 and 5, respectively, the sample sizes for the rest trials were greater than 16. Based on our empirical results, the sample sizes in the TAA AQ data seemed to be large enough so that t distributions were well approximated by normal distributions in the meta-analytic regression models. Finally, we did conduct a sensitivity analysis on the specification of hyperparameters in the priors of Eqs. (9) and (10). We empirically observed that the posterior estimates of β were fairly robust to the specification of hyperparameters in $\pi(\beta|\Sigma_0)$, $\pi(\Omega|v_0, \Omega_0)$, and $\pi(\sigma_{jk}^2 | a, b)$; however, the DICs were robust only to the specification of hyperparameters in $\pi(\beta|\Sigma_0)$ and $\pi(\sigma_{jk}^2 | a, b)$ but not to the specification of (v_0, Ω_0) . For

example, for Covariates Model 1, when a proper $\text{Inv-Wishart}_{v_0}(\Omega_0^{-1})$ prior with $v_0 = 2$ and $\Omega_0 = 001I_2$ was specified for Ω , the DIC and p_D were 56.73 and 7.29 under model (1) and both values were greater than these under the improper $\text{Inv-Wishart}_{v_0}(\Omega_0^{-1})$ prior. Thus, in order to obtain a DIC value, which is similar to AIC, a relatively vague prior should be specified for $\pi(\Omega | v_0, \Omega_0)$.

In all the Bayesian computations, we used 50,000 Gibbs samples after a burn-in of 1000 for each model, to compute all the posterior estimates, including posterior means, posterior standard deviations (SDs), 95% HPD intervals, and DICs. Codes were written for the FORTRAN 95 compiler, and we used IMSL subroutines with double precision accuracy. The convergence of the Gibbs sampler was checked using several diagnostic procedures as recommended by Cowles and Carlin (1996). The HPD intervals were computed by the Monte Carlo method developed by Chen and Shao (1999).

6. DISCUSSION

In this paper, we proposed two types of multidimensional random coefficients regression models and examined the connections between these two types of models via both profile likelihood and Bayesian approaches. From our theoretical and empirical investigations, a meta-analysis based on a normal random effects model with a known error variance for an aggregate response is valid when the sample sizes of trials included in a meta-analysis are reasonably large. In addition, the appropriate DICs were developed for comparing various covariates models, as well as two types of multidimensional random coefficients regression models. Based on the TAA AQ data with nine trials, we found that a single random intercept was not sufficient to capture heterogeneity in the meta-data and gender effect was not significant.

For the TAA AQ data, we implemented model (1) and Model (3) and (4) in WinBUGS. We found that only a proper $\text{Inv-Wishart}_{v_0}(\Omega_0^{-1})$ prior could be specified for Ω . For instance, in Covariates Model 1 with $v_0 = 2$ and $\Omega_0 = 001I_2$, the posterior means, SDs, and 95% credible intervals of the regression coefficients from WinBUGS were -2.007 , 0.094 , and $(-2.200, -1.819)$ for intercept; -0.639 , 0.086 , and $(-0.812, -0.468)$ for $\log(\text{dose} + 1)$; and -0.004 , 0.042 , and $(-0.086, 0.077)$ for gender under model (1). These values were similar to those in Table 2. However, WinBUGS gave a DIC value of 40.02 with $p_D = 15.52$ for this model. Notice that the DIC in WinBUGS was based on the deviance function defined as

$$-2 \log \left(\prod_{k=1}^K \prod_{j=1}^{m_k} \left[\frac{w_{jk}^{1/2}}{\sqrt{2\pi}} \exp \left\{ -\frac{w_{jk}}{2} (y_{jk} - \mathbf{x}'_{jk}\boldsymbol{\beta} - \mathbf{z}'_{jk}\boldsymbol{\gamma}_k)^2 \right\} \right] \right).$$

In this DIC calculation, the random coefficients $\boldsymbol{\gamma}_k$ were treated as “parameters,” which yielded a much larger p_D compared to the DIC defined by Eqs. (16) and (17).

Although model (3) and (4) was proposed only for a univariate aggregate response, this model can be extended to multiple aggregate responses if a study-level sample covariance matrix of multiple aggregate responses is available. If study-level correlations among multiple aggregate responses are not available, the extension of model (3) and (4) to multiple

aggregate responses is still possible but quite challenging. This leads to a new research project under investigation currently.

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Figure 1. Forest plots of trials with dosages stratified by gender, where each line corresponds to mean change in Nasal Index Score from baseline ± 1.96 standard error.

Table 1

Values of DIC for the TAA AQ data

Covariates model	x	z	DIC values	
			Model (1)	Model (3) and (4)
1	(1, log(dose + 1), gender)	(1, log(dose + 1))	54.80	54.34
2		(1)	64.03	61.57
3	(1, log(dose + 1), gender, log(dose + 1) $\times$ gender)	(1, log(dose + 1), log(dose + 1) $\times$ gender)	56.23	55.45
4		(1, log(dose + 1))	56.28	55.60
5		(1)	63.89	61.75
6	(1, log(dose + 1), log(dose + 1) ² , gender, log(dose + 1) $\times$ gender, log(dose + 1) ² $\times$ gender)	(1, log(dose + 1), log(dose + 1) ² , log(dose + 1) $\times$ gender, log(dose + 1) ² $\times$ gender)	57.85	57.24

Table 2

Parameter estimates for the TAA AQ data

Model	Variable*	Posterior estimate			MLE or PMLE		
		Estimate	SD	95% HPD interval	Estimate	SE	p-value
(1)	Intercept	-2.011	0.107	(-2.234, -1.806)	-2.015	0.094	<0.001
	Log(dose + 1)	-0.637	0.092	(-0.817, -0.449)	-0.631	0.082	<0.001
	Gender	-0.005	0.042	(-0.088, 0.077)	-0.006	0.042	0.890
	Ω_{00}	0.095	0.102	(0.002, 0.277)	0.060	0.042	0.190
	Ω_{01}	-0.061	0.087	(-0.231, 0.059)	0.019	0.025	0.479
	Ω_{11}	0.147	0.131	(0.005, 0.380)	0.043	0.027	0.161
(3) and (4)	Intercept	-2.007	0.105	(-2.219, -1.797)	-2.013	0.092	<0.001
	Log(dose + 1)	-0.640	0.092	(-0.825, -0.458)	-0.633	0.083	<0.001
	Gender	-0.006	0.043	(-0.089, 0.081)	-0.006	0.043	0.897
	Ω_{00}	0.086	0.104	(0.001, 0.259)	0.056	0.041	0.215
	Ω_{01}	-0.059	0.087	(-0.225, 0.054)	0.019	0.025	0.468
	Ω_{11}	0.145	0.132	(0.003, 0.371)	0.043	0.028	0.166

* All covariates in the models were standardized and specifically, log(dose + 1) and gender were subtracted by 3.0175 and 0.5 and then divided by 2.5018 and 0.5055, respectively.