Original Article

A Poisson Mixed Effects Model for Investigating the Exposure-by-Cohort Interaction: A Gibbs Sampling Approach

Seitaro Yoshida^{*1}, Yutaka Matsuyama^{*1}, Yasuo Ohashi^{*1} and Hirotsugu Ueshima^{*2}

^{*1}Department of Biostatistics, School of Health Sciences and Nursing,
University of Tokyo

^{*2}Department of Health Science, Shiga University of Medical Science
e-mail:seitaro@epistat.m.u-tokyo.ac.jp

A meta-analysis is a useful method for taking the findings of many studies and combining them in the hopes of identifying consistent patterns and sources of disagreement among those findings. While we interpret the average exposure effect, it is necessary to examine the homogeneity of the observed exposure effects across cohort, that is, exposure-by-cohort interaction. If the homogeneity is confirmed, the conclusions concerning exposure effects can be generalized to a broader population. In this paper, a Poisson mixed effects model is used to investigate the cohort effects on the exposure as well as on the baseline risk. The marginal posterior distributions are estimated by a Markov Chain Monte Carlo method, i.e. the Gibbs sampling, to overcome current computational limitations. We illustrate the methods with analyses of data from the Japan Arteriosclerosis Longitudinal Study, in which the effects of smoking on stroke events are examined based on the individual data of 23,860 subjects among 10 cohorts.

Key words: exposure-by-cohort interaction, Generalizability, Gibbs sampling, Poisson mixed effects model.

1. Introduction

Smoking is known to be associated with an increased risk of cardiovascular disease (Peto 1994). Although many epidemiologic studies in Western populations have also identified smoking as an independent risk factor for stroke (Colditz et al. 1988; Wolf et al. 1988; Shinton and Beevers 1989), its relationship in Japanese people living in Japan remains inconclusive (Hirayama T 1981; Nakayama T et al. 1977; Kiyohara et al. 1990; Tanizaki et al. 2000; Yamagishi et al. 2003; Mannami et al. 2004; Ueshima et al. 2004; Iso et al. 2005).

A meta-analysis is a useful method for taking the findings of many studies and combining them, in the hopes of identifying consistent patterns and sources of disagreement among those findings. When conducting a meta-analysis, as many authors have stressed (Rothman et

al. 2008), analysis of heterogeneity can be the most important function of meta-analysis. There is ordinarily no basis for assuming that the relative risk is constant across study cohorts. In fact, there are many situations that imply heterogeneity; for example, study cohorts are different not only in distributions of background factors such as age and sex, but also in environmental factors such as weather conditions and dietary habits, which are difficult to account for explicitly in the analysis.

The standard form of heterogeneity analysis is to regard the cohort as a stratification variable, that is, fixed effects, and to examine the exposure-by-cohort interaction by the analogy with ANOVA F-tests for interaction. However, small numbers of events per cohort and large numbers of confounders are often the case in most epidemiologic studies. In such cases, the loss of efficiency of analysis may be severe, if the cohort effects are taken to be fixed ones. Alternatively, in this article, we treat the cohort effects to be random ones in order to investigate the cohort effects on the exposure risk as well as on the baseline risk. The resulting statistical model for the observed data is a mixed effects model (Fitzmaurice et al. 2004; Greenland 2000), with the effects of exposure being fixed and the effects of cohort being random.

In some special cases such as the linear mixed effects model, the integral involved the likelihood function has a closed form, and ordinary iterative algorithms for maximizing the likelihood are used to obtain maximum likelihood or restricted maximum likelihood estimates for unknown model parameters (Laird and Ware 1982). For most nonlinear models such as the logistic and Poisson model, however, the likelihood function does not have an analytical form. Thus, one of the problems for fitting the generalized linear mixed effects model is the difficulty of the estimation of model parameters due to the requirement of the numerical integration techniques for calculation of the log-likelihood (Breslow and Clayton 1993). A variety of numerical approximation methods for maximizing the likelihood have recently been implemented in commercial software packages. For example, PROC NLMIXED in SAS directly maximizes an approximate integrated likelihood where the integration over the random effects is achieved using Gaussian quadrature (Pinheiro and Bates 1995). PROC GLIMMIX in SAS uses the linearization (Taylor series) methods known as restricted pseudo-likelihood estimation with an expansion around the current estimate of the best linear unbiased predictors of the random effects (Breslow and Clayton 1993; Wolfinger and O'Connell 1993).

As Fitzmaurice et al. (2004) have commented concerning the use of the above procedures, convergence of the algorithms should never be taken for granted, that is, neither should convergence to a global maximum be assumed. Their limited experience with these procedures indicates that it can be very sensitive to poor choices of starting values and/or the numerical accuracy of the quadrature used. In fact, in the analyses of the Japan Arteriosclerosis Longitudinal Study (JALS) data which are motivated example in this paper and are described in the next section, the algorithms by the NLMIXED/GLIMMIX procedures did not converge. For

this estimation problem with intractable high-dimensional integrals involved in the likelihood, Bayesian approaches have been proposed to avoid the need for numerical integration by taking repeated samples from the posterior distributions (Zeger and Karim 1991).

In this paper, we propose to use a Poisson mixed effects model to investigate the exposure-by-cohort interaction, and use a Gibbs sampling technique for model parameter inferences.

2. Methods

2.1 Study Population

The aim of the Japan Arteriosclerosis Longitudinal Study (JALS) is to investigate the risk factors for arteriosclerotic disease specific to Japanese population (Japan Arteriosclerosis Longitudinal Study (JALS) Group. 2008). The JALS is composed of two studies: one is a pooled study based on individual patient data of existing prospective cohort studies in Japan, which has been conducted between 1985 and December 2001, the other is a prospective cohort study, which is on-going since 2004. In this paper, we used data from the former study, in which a total of 66,691 men and women with baseline records on such as age (year), gender, BMI (body mass index) (kg/m^2) and history of smoking were registered in 17 regional cohorts and 4 occupational cohorts. The subjects had also several medical check-up data including medical history and laboratory tests.

In this paper, we excluded following subjects from the analyses; those who belonged to the occupational cohorts, because our focus was on the regional cohorts, those who belonged to the regional cohorts where data on stroke event was not observed, those aged under 40 or over 90 years old, because of the small numbers of subjects and stroke events in those age categories, those who with a history of stroke, and those who have missing data on a history of smoking and confounders. The final analysis population consisted of 9,087 men and 14,773 women in 10 cohorts. The endpoint was the first occurrence of stroke, comprising fatal and nonfatal event of ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage. All outcomes were classified according to the ICD-9 (9th revision of the International Classification of Diseases) until the end of 1994, and according to the ICD-10 since the beginning of 1995.

2.2 A Poisson Mixed Effects Model

We propose to use a Poisson mixed effects model to investigate a smoking-by-cohort interaction adjusted for age (< 65 or ≥ 65 years), SBP (systolic blood pressure; < 140 or ≥ 140 mmHg), BMI (< 25 or ≥ 25 kg/m^2), current alcohol drinking status (yes or no) and history of DM (diabetes mellitus; present or absent). All analyses were stratified by gender.

A form of the Poisson mixed effects model used for the analyses can be expressed as,

$$\log E(y_{ij} | b_i) = \log t_{ij} + \beta_0 + \beta_1 x_{ij} + \gamma z_{ij} + b_{0i} + b_{1i} x_{ij} \quad (1)$$

where y_{ij} represents the event variable ($y_{ij} = 1$ if stroke is observed, $y_{ij} = 0$ otherwise) for the j th subject ($j = 1, \dots, n_i$) in the i th cohort ($i = 1, \dots, N$); t_{ij} represents the person-year of follow-up; Jpn J Biomet Vol.29, No.2, 2008

x_{ij} represents a smoking status; z_{ij} represents a vector of covariates stated above; the parameters β and γ represent the fixed effects corresponding to x_{ij} and z_{ij} , respectively; b_{0i} and b_{1i} represent the random effects for the i th cohort, which are assumed to be normally distributed,

$$\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} \sim N \left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} d_{11} & d_{12} \\ d_{12} & d_{22} \end{pmatrix} \right]. \quad (2)$$

In the model (1), the random effect b_{0i} is the deviation of the i th cohort from a baseline risk, while b_{1i} is the deviation of the i th cohort from an average smoking effect β_1 , that is, smoking-by-cohort interaction.

2.3 Full Conditional Distributions for Each Parameter

The Gibbs sampling is simply a technique for generating random variables from a difficult joint distribution indirectly without calculating the density. The mechanism is based only on elementary properties of Markov chains (Gelfand and Smith 1990). Gilks et al. (1993) have reviewed some applications of the Gibbs sampling to Bayesian models in medicine. To perform the Gibbs sampling, we require the full conditional distributions for each of the unknown parameters of the model.

In the Bayesian approach to analyzing the model (1), the parameters $\alpha = (\beta, \gamma)$ and D are random variables and treated symmetrically with the observed y and unobserved b_i . The marginal posterior distribution over the random effects corresponding to the model (1) is proportional to

$$f(\alpha, D | y) = \prod_{i=1}^N \int f(y_i | \alpha, b_i) \times |D|^{-1/2} \exp\left(-\frac{1}{2} b_i^T D^{-1} b_i\right) \pi(\alpha, D) db_i, \quad (3)$$

where $f(y_i | \alpha, b_i)$ is the conditional Poisson likelihood given b_i with mean expressed through (1), D is the variance-covariance matrix for b_i , and $\pi(\alpha, D)$ is the joint prior distribution for α and D . The necessary full conditional distributions for model (3) at iteration k ($k = 1, \dots, K$) are given as follows.

2.3.1 Sampling of the Fixed Effects

Given the random effects $b_i^{(k)}$, the Poisson mixed effects model (1) reduces to the usual Poisson regression model with offset $b_{0i}^{(k)} + b_{1i}^{(k)} x_{ij}$ for each subject. If we assume a uniform prior for α , the full conditional posterior distribution for α is proportional to the Poisson likelihood function $\prod_{i=1}^N \prod_{j=1}^{n_i} f(y_{ij} | b_i^{(k)})$. In larger samples, this can be closely approximated by a multivariate normal distribution with mean vector $\hat{\alpha}^{(k)}$, the maximum likelihood estimate, and covariance matrix $\hat{V}_{\hat{\alpha}}^{(k)}$, the inverse of the corresponding observed Fisher information. That is, to sample from full conditional distributions for α at iteration k , we find $\hat{\alpha}^{(k)}$ and $\hat{V}_{\hat{\alpha}}^{(k)}$ by performing Poisson regression of y_{ij} on x_{ij} using the simulated (fixed) values $b_{0i}^{(k)} + b_{1i}^{(k)} x_{ij}$ as offsets and generate a random variate $\hat{\alpha}^{(k+1)}$ from a multivariate normal distribution $N(\hat{\alpha}^{(k)}, \hat{V}_{\hat{\alpha}}^{(k)})$.

2.3.2 Sampling of the Random Effects

The full conditional posterior distribution for b_i does not have a closed form and we cannot draw samples directly from its distribution, because it involves the same intractable integral with respect to b_i that we avoided in the maximum likelihood analysis. The distribution can be expressed as

$$\frac{f(y_i | \alpha, b_i)g(b_i | D)\pi(\alpha, D)}{\int f(y_i | \alpha, b_i)g(b_i | D)\pi(\alpha, D)db_i}, \quad (4)$$

where $g(b_i | D)$ is the normal density given in (2). Although the numerator in (4) is easily evaluated, the scale factor in the denominator cannot be evaluated explicitly. In Gibbs sampling, however, only a random variable from the conditional distribution is needed. It can be obtained using random variate generating methods such as rejection sampling without evaluating the integral. We used the normal rejection sampling method of Zeger and Karim (1991). Their method is to find the mode and curvature of the numerator of (4), call it $p_i(b_i)$, and to match a Gaussian kernel with the covariance matrix multiplied by an inflation factor to $p_i(b_i)$. This Gaussian kernel is then rescaled to be at least as large as $p_i(b_i)$ at the mode, and used as the envelope function. We used SAS/IML nonlinear optimization subroutines, Newton-Raphson optimization, to find the mode and curvature of $p_i(b_i)$, and a variance inflation factor of 2.5 was used.

2.3.3 Sampling of the Random Effects Variance

We have assumed that the random effects b_i are independent normal $N(0, D)$ random variables. A non-informative prior for D is $P(D) \propto |D|^{-\frac{q+1}{2}}$, where $q = 2$ in the model (1). Then the full conditional posterior distribution of D^{-1} follows a Wishart distribution with parameter matrix $(\sum_{i=1}^N b_i b_i^T)^{-1}$ with $(N - q + 1)$ df (Gelman et al. 2004). Simulation from the Wishart distribution for 2×2 matrix D^{-1} is easily accomplished using the algorithm of Odell and Feiveson (1966). Their algorithm is as follows: with $Ga(\cdot, \cdot)$ and $N(\cdot, \cdot)$ denoting gamma and normal distributions, respectively, draw independently from $U_1 \sim Ga(\frac{\nu}{2}, \frac{1}{2})$, $U_2 \sim Ga(\frac{\nu-1}{2}, \frac{1}{2})$, and $U_3 \sim N(0, 1)$, set

$$W = \begin{pmatrix} U_1 & U_3\sqrt{U_1} \\ U_3\sqrt{U_1} & U_2 + U_3^2 \end{pmatrix},$$

then if $S^{-1} = (H^{1/2})^T (H^{1/2})$, $D^{-1} = (H^{1/2})^T W (H^{1/2}) \sim \text{Wishart}(S^{-1}, \nu)$.

2.4 Implementation of the Gibbs Sampling

The estimation of model parameters was conducted using SAS/IML (SAS Institute Inc., Cary NC). We simulated independent sequences of length 2,000 with three kinds of starting values, where the procedure entailed sampling from 1,000 post-convergence iterations in each sequence, thus yielding 3,000 total iterations upon which we based our posterior estimates. We set three kinds of initial values of the random effects variances (d_{11}, d_{12}, d_{22}) at $(1.0, 0, 0.1)$,

(0.1, 0, 0.6), (0.1, 0, 1.0), respectively. First one represents the large baseline risk and small interaction effect, second one represents small baseline risk and medium interaction effect, and third one represents small baseline risk and large interaction effect. For the random effects, initial values were drawn from the multivariate normal distribution (2) with each initial value of the random effects variances.

Convergence of the Markov chains was assessed by the Gelman-Rubin statistic, that is, potential scale reduction (PSR) factor (Gelman and Rubin 1993). Details of the PSR are given in Appendix.

3. Results

Table 1 and 2 show the baseline and stroke events characteristics of the analysis 10 cohorts, respectively. The total number of stroke events was 345 among 9,087 men (3.8%) and 368 among 14,773 women (2.5%). The total incidence rate (/year) for stroke events was 4.59×10^{-3} in men and 2.90×10^{-3} in women, where substantial variations across cohorts were seen in women. The incidence rate ratios (IRRs) for current smoking were not consistent across cohorts, particularly, in women.

Table 3 shows the posterior summaries of the model parameters in (1). The last column in Table 3 shows the estimate of PSR comparing three runs for each of several model parameters. The estimates were all near 1, indicating that convergence occurred for these parameters. Table 4 shows the estimates of IRR for each fixed effects parameter. After adjustment of age, SBP, BMI, current alcohol drinking status and history of DM, an association between current smoking status and stroke events was observed among men (IRR = 1.55, 95% confidence region (CR) = 1.22-2.02), while the significant association was not observed among women (IRR = 1.32, 95% CR = 0.76-2.18).

In Table 4, results from the ordinary Poisson model are also shown, that is, estimates of IRR based on the fixed effects model where random effect terms were excluded from the model (1). The posterior features for smoking effects changed little compared with the ordinary model ignoring cohort effects. This indicates that incorporating cohort effects was not critical for drawing conclusions on the overall smoking effects. However, the mixed effects model can be used to evaluate the cohort effects on the smoking risk as well as on the baseline risk.

The posterior summaries of the random effects variances, which represent the volumes of cohort differences, are also shown in Table 3. For both genders, baseline variability (d_{11}) was larger than variability of smoking effect (d_{22}). The variances in women were larger than those of men in both risks. Because the random effects were assumed to be normally distributed in (2), the posterior mean of the variance of random effects indicates that 95% of cohorts have the baseline risk ($\exp(\pm 1.96\sqrt{\hat{d}_{11}})$) in the range 0.48 to 2.08 for men and 0.34 to 2.98 for women. Likewise, the variability of smoking-by-cohort interaction ($\exp(\pm 1.96\sqrt{\hat{d}_{22}})$) was in the range

Table 1. Characteristics of analysis 10 cohorts stratified by gender.

Gender	Cohort	Number of subjects	Follow-up period(year)		Age(year)		SBP(mmHg)		BMI(kg/m ²)		Current smoking		Current drinking		DM	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	N	%	N	%	N	%
Men	1	670	6.2	59.9	10.6	13.2	19.7	3.2	23.7	3.2	341	50.9	448	66.9	40	6.0
	2	466	11.3	56.3	13.3	13.4	16.3	2.9	23.5	2.9	229	49.1	289	62.0	7	1.5
	3	1086	10.4	55.8	10.8	13.7	20.1	2.9	22.9	2.9	679	62.5	839	77.3	113	10.4
	4	635	9.9	58.7	11.7	13.4	16.3	3.0	23.5	3.0	319	50.2	410	64.6	119	18.7
	5	1840	9.8	54.3	9.3	13.7	19.7	3.0	23.3	3.0	1150	62.5	1254	68.2	207	11.3
	6	1261	9.2	55.9	11.1	13.4	20.1	2.8	22.6	2.8	733	58.1	874	69.3	108	8.6
	7	1182	7.1	56.3	13.6	13.3	19.3	3.0	22.3	3.0	688	58.2	860	72.8	100	8.5
	8	977	5.0	58.3	12.3	13.2	17.7	2.9	23.2	2.9	391	40.0	652	66.7	77	7.9
	9	292	9.4	60.8	10.3	13.4	20.4	3.1	22.7	3.1	138	47.3	173	59.2	16	5.5
	10	678	3.7	63.1	10.6	13.6	20.3	3.0	23.2	3.0	250	36.9	499	73.6	47	6.9
Total		9087	8.3	57.1	11.6	13.5	19.3	3.0	23.0	3.0	4918	54.1	6298	69.3	834	9.2
Women	1	909	6.4	59.4	9.8	13.2	21.3	3.2	23.8	3.2	66	7.3	153	16.8	33	3.6
	2	958	12.1	55.7	11.9	13.1	15.2	3.5	24.3	3.5	15	1.6	13	1.4	6	0.6
	3	1439	10.8	56.0	10.7	13.3	18.9	3.4	24.0	3.4	31	2.2	41	2.8	77	5.4
	4	1204	10.7	57.2	10.4	13.0	16.4	3.4	24.6	3.4	29	2.4	90	7.5	187	15.5
	5	2510	10.1	54.7	9.5	13.6	19.7	3.4	23.9	3.4	165	6.6	201	8.0	152	6.1
	6	2438	9.8	52.7	10.6	13.1	20	3.0	22.6	3.0	259	10.6	372	15.3	99	4.1
	7	1661	7.3	56.4	14.1	13.1	19.9	3.4	22.8	3.4	151	9.1	402	24.2	66	4.0
	8	2200	5.3	52.3	13.6	12.4	19	3.2	22.8	3.2	93	4.2	318	14.5	66	3.0
	9	455	9.8	60.6	10.1	13.2	22.3	3.1	23.0	3.1	19	4.2	42	9.2	18	4.0
	10	999	3.8	61.9	10.9	13.2	20.9	3.2	23.0	3.2	20	2.0	259	25.9	38	3.8
Total		14773	8.6	55.6	11.7	13.1	19.6	3.3	23.4	3.3	848	5.7	1891	12.8	742	5.0

SBP: Systolic blood pressure; BMI: Body mass index; DM: Diabetes mellitus

Table 2. Stroke events of analysis 10 cohorts stratified by gender.

Gender Cohort		Stroke events N	%	Person-time (year)	Incidence rate (/year)	IRR for Current smoking
Men	1	27	4.0	4173	6.47×10^{-3}	0.79
	2	22	4.7	5278	4.17×10^{-3}	1.29
	3	56	5.2	11284	4.96×10^{-3}	1.44
	4	59	9.3	6285	9.39×10^{-3}	1.40
	5	68	3.7	17953	3.79×10^{-3}	1.83
	6	38	3.0	11633	3.27×10^{-3}	1.08
	7	31	2.6	8413	3.68×10^{-3}	2.03
	8	18	1.8	4925	3.65×10^{-3}	0.94
	9	14	4.8	2747	5.10×10^{-3}	1.19
	10	12	1.8	2542	4.72×10^{-3}	1.23
total		345	3.8	75233	4.59×10^{-3}	1.29
Women	1	27	3.0	5792	4.66×10^{-3}	0.52
	2	24	2.5	11553	2.08×10^{-3}	6.39
	3	58	4.0	15520	3.74×10^{-3}	0.90
	4	66	5.5	12940	5.10×10^{-3}	1.26
	5	70	2.8	25261	2.77×10^{-3}	1.35
	6	34	1.4	23915	1.42×10^{-3}	2.36
	7	38	2.3	12166	3.12×10^{-3}	0.91
	8	16	0.7	11664	1.37×10^{-3}	0.00
	9	31	6.8	4457	6.96×10^{-3}	0.77
	10	4	0.4	3782	1.06×10^{-3}	0.00
total		368	2.5	127050	2.90×10^{-3}	1.15

IRR: Incidence rate ratio

Table 3. Posterior summaries for the model parameters in (1).

Gender	Parameter	Mean	Standard deviation	2.5 percentile	97.5 percentile	PSR
Men	Intercept	-6.39	0.24	-6.85	-5.91	1.00
	Current smoking (yes vs no)	0.44	0.13	0.20	0.70	1.00
	Age (≥ 65 years vs < 65)	1.03	0.11	0.81	1.25	1.00
	SBP (≥ 140 mmHg vs < 140)	0.88	0.11	0.65	1.10	1.00
	BMI (≥ 25 kg/m ² vs < 25)	0.03	0.13	-0.22	0.28	1.00
	Current drinking (yes vs no)	-0.04	0.08	-0.21	0.13	1.00
	DM (present vs absent)	0.57	0.14	0.29	0.85	1.00
	d_{11}	0.14	0.23	0.01	0.63	1.01
	d_{12}	-0.01	0.07	-0.11	0.05	1.01
	d_{22}	0.03	0.10	0.00	0.17	1.14
Women	Intercept	-6.72	0.22	-7.15	-6.28	1.04
	Current smoking (yes vs no)	0.28	0.27	-0.28	0.78	1.04
	Age (≥ 65 years vs < 65)	1.20	0.12	0.97	1.43	1.04
	SBP (≥ 140 mmHg vs < 140)	0.87	0.10	0.67	1.07	1.04
	BMI (≥ 25 kg/m ² vs < 25)	0.22	0.11	0.00	0.44	1.04
	Current drinking (yes vs no)	-0.08	0.19	-0.45	0.31	1.04
	DM (present vs absent)	0.24	0.17	-0.11	0.58	1.04
	d_{11}	0.31	0.35	0.03	1.19	1.01
	d_{12}	-0.02	0.19	-0.48	0.30	1.00
	d_{22}	0.18	0.39	0.00	1.07	1.04

SBP: Systolic blood pressure; BMI: Body mass index; DM: Diabetes mellitus

PSR: Potential scale reduction

Table 4. Comparison of the results between mixed effects and ordinary Poisson model.

Gender	Parameter	Poisson mixed effects model		Ordinary Poisson model	
		IRR	95% CR	IRR	95% CR
Men	Current smoking (yes vs no)	1.55	1.22-2.02	1.53	1.22-1.91
	Age (≥ 65 years vs < 65)	2.79	2.24-3.49	2.86	2.29-3.57
	SBP (≥ 140 mmHg vs < 140)	2.41	1.91-3.01	2.38	1.91-2.96
	BMI (≥ 25 kg/m ² vs < 25)	1.03	0.80-1.32	1.05	0.82-1.35
	Current drinking (yes vs no)	0.96	0.81-1.14	0.96	0.76-1.20
	DM (present vs absent)	1.76	1.34-2.33	1.80	1.34-2.40
Women	Current smoking (yes vs no)	1.32	0.76-2.18	1.30	0.85-2.00
	Age (≥ 65 years vs < 65)	3.32	2.64-4.17	3.43	2.77-4.24
	SBP (≥ 140 mmHg vs < 140)	2.39	1.96-2.93	2.35	1.90-2.91
	BMI (≥ 25 kg/m ² vs < 25)	1.25	1.00-1.56	1.32	1.07-1.63
	Current drinking (yes vs no)	0.92	0.64-1.36	0.88	0.60-1.29
	DM (present vs absent)	1.27	0.90-1.78	1.37	0.97-1.95

IRR: Incidence rate ratio; CR: Confidence region; CI: Confidence interval
 SBP: Systolic blood pressure; BMI: Body mass index; DM: Diabetes mellitus

0.71 to 1.40 and 0.44 to 2.30, respectively.

Figures 1 and 2 summarize the posterior distributions of the cohort effects for the baseline risk and smoking effects, respectively. These are the box plots of the posterior sample values of generated ones for each of the 10 cohorts. The baseline risk, $\exp(b_{0i})$, is the deviation in the i th cohort from an overall baseline risk, and the smoking effect, $\exp(\beta_1 + b_{1i})$, is the deviation in the i th cohort from an overall smoking effect. Figure 1 indicates substantial variation in the baseline risk across cohorts, particularly in women. The baseline risk seems to vary considerably across cohorts (prior mean of the baseline risk is one). On the other hand, Figure 2 appears to indicate the homogeneity in the effect of smoking across cohorts in both genders, that is, there is little smoking-by-cohort interaction in this data. Thus, there is little difference in the smoking effects

Fig. 1. Posterior distribution of baseline risk ($\exp(b_{0i})$) in each cohort.

Fig. 2. Posterior distribution of smoking effect ($\exp(\beta_1 + b_{1i})$) in each cohort (smoking-by-cohort interaction).

on stroke events across cohorts and the smoking is shown to be an independent risk factor for the events, while there appears to be substantial variation in the baseline risk across cohorts. This result indicates that the observed smoking effects might be generalized to a broader population.

4. Discussion

In this paper, we proposed to use a Poisson mixed effects model (1) with two random effects to investigate the exposure-by-cohort interaction. It is important to investigate the cohort effects on the exposure risk in addition to the baseline risk. This model is useful not only for the meta-analysis of individual epidemiologic data like in the JALS, but also for the analysis of multicenter clinical trials (Matsuyama et al. 1998).

Until recently, a potential limitation of generalized linear mixed models was their computational burden. Because there is no simple closed-form solution for the marginal likelihood, numerical integration (Pinheiro and Bates 1995) or pseudo-likelihood (Breslow and Clayton 1993; Wolfinger and O'Connell 1993) techniques are required. Maximum or restricted maximum likelihood estimation has only recently been implemented in standard statistical software, for example, PROC NLMIXED or PROC GLIMMIX in SAS. However, problems with convergence are likely to arise when complicated models with two or three random effects are fitted (Fitzmaurice et al. 2004; Evans et al. 2001). This non-convergence problem seems to frequently occur in highly unbalanced data or in sparse data, that is, the number of events is small relative to the adjustment variables. In fact, in our data analysis of the JALS data, the number of stroke events was small in each cohort as shown in Table 2, and the optimization algorithms by the NLMIXED/GLIMMIX procedures for the model (1) did not converge, although a number of things was tried, for example, change the initial values by using a grid search specification to obtain a set of good feasible starting values, change or modify the update or optimization

technique, or change the convergence criterion.

To overcome the above non-convergence problems, we chose a Bayesian viewpoint and the Gibbs sampling was used for estimating procedures. The Gibbs sampling is a useful technique for estimating complex Bayesian models, although it is computationally intensive. So long as conjugate priors can be found for model parameters, the implementation of the Gibbs sampling is straightforward as illustrated in this paper. When conjugate priors cannot be available, especially in generalized linear models or non-linear models, random variate generating technique can be used. In this paper we used a rejection sampling (Zeger and Karim, 1991), although it involved many evaluations of target distribution.

Another advantage of the Gibbs sampling is its flexibility. For example, the prior distribution for the random effects need not be the Gaussian as in the usual mixed effects model. The use of a limited class of distributions results in a limited and potentially inappropriate inferences. To account for outliers, it can be applied to the heavy-tailed multivariate random effects such as t -distribution with a small value of degrees of freedom (Matsuyama et al. 1998).

Bayesian approach described in this paper has other advantages and flexibilities over that of frequentist. For example, if we have some background information on the fixed effects, we can utilize such information explicitly in the analyses through the prior distributions. Greenland (2000) proposed the active use of the Bayesian viewpoints in the analyses of epidemiologic data. In this paper, because we do not have firm such information on the effects of fixed effects parameters, we set non-informative priors, therefore, our results via the Gibbs sampling were virtually identical with those of the maximum likelihood methods.

In conclusions, we proposed to use a Poisson mixed effects model for investigating the exposure-by-cohort interaction, and use a Gibbs sampling technique for model parameter inferences. It was found from the analyses of the JALS data for the association between smoking and stroke events that substantial variations across cohorts were seen in the baseline risk, but not in the effect of smoking. This result indicates that the observed smoking effects might be generalized to a broader population.

Acknowledgements

We would like to express gratitude toward the Japan Arteriosclerosis Longitudinal Study Group (Principal Investigator: Hirotsugu Ueshima M.D. PhD.) for permission to use these valuable study data. We would also like to thank two referees for their many helpful comments and suggestions.

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Appendix

Calculation of the Gelman-Rubin's Potential Scale Reduction

Let m be the number of independent parallel sequences and n be the length of each sequence after discarding the first half of the simulations. For each parameter ψ_{ij} ($i = 1, \dots, m$; $j = 1, \dots, n$), we compute B and W , the between- and within-sequence variance;

$$B = \frac{n}{m-1} \sum_{i=1}^m (\bar{\psi}_{i.} - \bar{\psi}_{..})^2, \quad \text{where} \quad \bar{\psi}_{i.} = \frac{1}{n} \sum_{j=1}^n \psi_{ij}, \quad \bar{\psi}_{..} = \frac{1}{m} \sum_{i=1}^m \bar{\psi}_{i.}$$

$$W = \frac{1}{m} \sum_{i=1}^m s_i^2, \quad \text{where} \quad s_i^2 = \frac{1}{n-1} \sum_{j=1}^n (\psi_{ij} - \bar{\psi}_{i.})^2$$

From the two variance components, we estimate the marginal posterior variance of each scalar summary ψ ;

$$\hat{V}(\psi) = \frac{n-1}{n} W + \frac{1}{n} B,$$

which overestimates the marginal posterior variance, but is unbiased in the limit as $n \rightarrow \infty$. Then we monitor convergence of the simulation by estimating the factor by which the scale of the current distribution for ψ might be reduced;

$$\sqrt{\hat{R}} = \sqrt{\frac{\hat{V}(\psi)}{W}}$$

This PSR is the ratio of the estimated upper to lower bounds for the standard deviation of ψ . This statistics can be calculated sequentially as the runs proceed, and declines to 1 as the runs converge; the closer the estimate is to 1.0 the more likely is the Gibbs sampling to have converged.