COMPARING BAYESIAN AND CLASSICAL METHODS

IN THE ANALYSIS OF

A CLUSTER RANDOMIZED TRIAL

COMPARING BAYESIAN AND CLASSICAL METHODS IN THE ANALYSIS OF A CLUSTER RANDOMIZED TRIAL

(THE COMMUNITY HYPERTENSION ASSESSMENT TRIAL)

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Abstract

Cluster randomized controlled trials are increasingly used to assess the effectiveness of life-style interventions in improvement of health services or prevention of disease. However, statistical methods in the analysis of cluster randomized controlled trials are not well established especially for analyzing binary outcomes.

This project is motivated by the Community Hypertension Assessment Trial (CHAT) to assess the effectiveness of a 12-month community-based blood pressure management program in improving the management and monitoring of high blood pressure (BP) among older people. The study is a paired cluster randomized controlled trial, where the family physicians' practices are the clusters randomly allocated to CHAT intervention or usual practice, and a random sample of 55 patients 65 years and older were selected from the 14 practices in each study arm for health record review. The primary outcome was controlled BP over 12 months defined as systolic BP ≤ 140 and diastolic BP ≤ 90 for patients without diabetes or target organ damage or systolic BP ≤ 130 and diastolic BP ≤ 80 for patients with diabetes or target organ damage. Secondary outcomes include frequency of BP monitoring and average BP over a 12 month period.

The clinical objective of this project is to evaluate the effectiveness of the CHAT intervention. The statistical objective is to compare Bayesian and classical methods of analyzing cluster-randomized trials using CHAT study as an example. We compared the results of different cluster-level analysis methods: i) un-weighted

regression, ii) weighted regression, iii) random-effects meta-analytic approach, and different individual-level analyses: i) standard logistic regression, ii) robust standard errors approach, iii) generalized estimating equations, iv) random-effect logistic regression, v) Bayesian random-effect regression.

We find that there is no sufficient evidence in support of the effectiveness of the CHAT intervention on all outcomes. For BP control, odds ratio (95% confidence interval) is 1.14 (0.72, 1.80) from generalized estimating equations. This result remains robust under different methods. We also find that the results from different statistical methods are different. The results from cluster-level analysis methods are quite different, while the results from the individual-level analysis methods are similar.

We conclude that using various methods to analyze the trial provide good sensitivity analyses to help in interpreting the results of cluster randomized trials. Extensive simulation studies comparing the statistical powers of the different methods in different situations are required.

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Chapter 1

Introduction

1.1 The CHAT Trial

The prevalence of high blood pressure (BP) is about 22% among Canadian adults and it increases with age [1]. In Canada, within the age group from 65 to 74 years, 58% of females and 56% of males have mean BP $\geq$ 140/90 mmHg [2]. Hypertension is a modifiable risk factor for cardiovascular diseases including stroke [3], kidney disease [1] and Alzheimer's disease [4-5]. Even though BP health services are available throughout the community, it remains one of the most significant and costly health problems facing Canadians. Many researchers are trying to find an optimal way to organize and deliver the health care to patients with high BP [6-10].

According to the review report on interventions used to improve control of blood pressure in patients with hypertension [11], the majority of randomized controlled trials [12-16] are associated with improved BP control comparing the health professional led care to the usual care. However, further investigation and evaluation are required.

The Community Hypertension Assessment Trial (CHAT) was designed and conducted to evaluate the effectiveness of community pharmacy BP clinics linked with

family practices (FP) on monitoring and management of high BP among older adults [1].

The CHAT was a multi-center, paired cluster randomized controlled trial using blocked stratified cluster randomization. The participants of the CHAT trial included family physicians (FP), patients, pharmacies, health personnel, and peer volunteers in the cities of Hamilton and Ottawa. FP was the unit of randomization. Eligible physicians were those who had a non-academic, full-time, regular family practice in terms of size of patient population and case mix, and were able to provide a roster of their regular patients aged 65 and over. Eligible patients must be community-dwelling patients with at least 65 years and be able to visit the community pharmacy. Eligible FPs were stratified according to two criteria: First, the median number of patients in the practices with adequate BP control. Second, the median number of patients aged 65 years and older according to the baseline chart review. FPs within each stratum were randomly allocated to the intervention or control group, therefore 1:1 distribution of FPs below and above the median at baseline was achieved. Patients from the same FP were allocated to the same treatment. The design of the study is summarized in Figure 1 in Appendix D.

Patients allocated to the intervention group were invited to the BP clinic in the pharmacy. The BP clinic staff measured the BP of the patients and reviewed cardiovascular risk factors with patients with high BP readings. They then faxed the patients' information to the FP's office. Patients allocated to the control group got usual

care at their FP's office. The detailed comparison of the intervention and control is presented in Figure 2 in Appendix D.

The health records of the patients were collected at baseline and 12 months after the intervention, i.e. the end of the trial, through the chart review. The primary outcome was controlled BP over 12 months defined as systolic BP $\leq$ 140 mmHg and diastolic BP $\leq$ 90 mmHg for patients without diabetes or target organ damage or systolic BP $\leq$ 130 mmHg and diastolic BP $\leq$ 80 mmHg for patients with diabetes or target organ damage. The definitions of the primary outcomes are presented in Table B1 in Appendix B. Secondary outcomes included BP monitored (binary), BP monitoring frequency (count), mean systolic BP (continuous), mean diastolic BP (continuous), percentage of patients with BP controlled (continuous), difference of percentage of patient with BP controlled between baseline and the end of the trial (continuous). The definitions of the secondary outcomes are presented in Table C1 in Appendix C.

In the CHAT trial, 28 FPs and 55 patients from each FP participated in the study. Fourteen of the FPs were randomly allocated to the intervention and control groups respectively. Patients from the same FP were assigned to the same treatment. Therefore, the total number of participants was 1540, and the number of patients allocated to each treatment arm was 770. This sample size was calculated to detect a minimal clinically important difference of 20% (two sided) between the intervention and control groups at significance level of 5% and power of at least 80%. To estimate the sample size, we assumed that the intra-cluster correlation coefficient (ICC) was

0.13, which was obtained based on the information from the pilot study (the SMART data).

1.2 Objective of the Report

Cluster randomized control trials are increasingly being used in health care. Motivated by the CHAT study to assess the effectiveness of the intervention relative to the control in improving the monitoring and management of high blood pressure among older adults, we explore the differences between statistical methods in analysis of cluster randomized trials.

The clinical objective of this thesis is to assess the impact of CHAT intervention in improving the patients' blood pressure compared to the control. To achieve this goal, we applied four cluster-level, four individual-level and one Bayesian individual-level analysis methods and some other parametric and non-parametric methods to the CHAT data. The results from the analysis will help health researchers to develop an effective and practical solution to the challenges of regular monitoring of the BP among older adults.

The statistical objective of this thesis is comprised of three parts. First, compare the results from the individual-level versus the cluster-level analysis methods. Second, compare the results from classical statistical methods with the results from the Bayesian analysis. Third, investigate the differences of the statistical methods in analysis of cluster randomized trials and discuss the robustness of different methods based on a sensitivity analysis. Many statistical methods are available to analyze cluster

randomized trials at both cluster-level and individual-level [17-18]. However, the efficiency and consistency using different analytical methods, especially the methods for analyzing binary outcomes, have received little attention. The comparisons and discussions in this thesis provide insights into analysis of cluster randomized trials.

1.3 Scope of the Report

In this thesis, we first briefly introduce the background and design of the CHAT trial. Using the CHAT trial as an example, we then discuss the cluster-level and individual-level statistical methods in analysis of cluster randomized controlled trials for both the binary and continuous outcomes. We also report the results of the CHAT trial from all the statistical methods. We compare the results from different statistical methods and investigate why they differ. Finally, we make conclusions based on our results and discussions.

Specifically, in Chapter 2 we briefly review all the statistical methods which we apply to the CHAT data in the analysis of this cluster randomized trial. We illustrate how each statistical method handles the clustering of the data. These statistical methods include some classical methods and a Bayesian method. We also discuss the sensitivity analysis of the Bayesian models.

In Chapter 3, we report and compare the results for primary and secondary outcomes of the CHAT trial from different statistical methods. We present the results

from the Bayesian method when assuming different prior distributions for the variance of the cluster-level random effect.

In Chapter 4, we present our key findings in the analysis of the CHAT trial. We also discuss the reasons of why different methods give different results. In addition, we point out the strength and limitations in the design of the CHAT trial and compare our results for the CHAT trial with the results for other similar trials. We also discuss the robustness of the Bayesian model.

Finally, in Chapter 5, we draw conclusions and provide some suggestions on analyzing cluster randomized controlled trials based on our findings and results.

Chapter 2

Statistical Methods

2.1 Overview

In this section, we provide an overview of the statistical methods used to analyse both primary and secondary outcomes. We also describe the sensitivity analysis for the Bayesian model. In addition, since the randomization unit is cluster (FP), it is important to check the balance of the demographic and baseline diagnostic characteristics of the patients between the intervention and control groups.

The demographic and baseline diagnostic characteristics of the patients were analysed using descriptive statistics presented as mean (standard deviation) or median (minimum, maximum) for continuous variables and count (percent) for categorical variables.

The analysis of primary and secondary outcomes was done using intention-to-treat (ITT) analysis. For each primary outcome, eight classical methods and one Bayesian method were applied to analyze the CHAT data. The classical methods used in this report included four cluster-level statistical methods and four individual-level statistical methods. The cluster-level methods were un-weighted regression, weighted regression, random-effect meta-regression without adjustment for variance inflation

factor (VIF) and random-effect meta-regression with adjustment for VIF. The four individual-level methods were standard logistic regression [19-20], robust standard error, generalized estimating equations (GEE), and random-effect logistic regression. The Bayesian approach used in this thesis is Bayesian random-effect logistic regression, which was also an individual-level method. We also performed sensitivity analysis for Bayesian random-effect model to assess the impact of choosing different priors for the primary outcome — BP controlled. For secondary outcomes, we also used two-sample t-test [21] and Mann-Whitney *U* test (Wilcoxon rank sum test) [21].

All classical analyses were performed using SAS Version 9.0 and Bayesian analysis was performed using WinBugs Version 1.4. The results of the analyses for binary outcomes are reported as odds ratio (OR), corresponding 95% confidence interval (CI) and associated *p*-values. For analysis of continuous outcomes, the results are reported as estimate of treatment effect (coefficient), corresponding 95% CI and associated *p*-values. *P*-values are reported to three decimal places with *p*-values less than 0.001 reported as $p<0.001$.

The reporting of the results follows the CONSORT (Consolidated Standards of Reporting Trials) statement guidelines for reporting cluster-randomized trials [22] and ROBUST guideline [23] for reporting Bayesian analysis. The general schema of study analysis is described at Figure 3 in Appendix D. The code for running classical statistical models on SAS and Bayesian models on WinBugs along with the initials are presented in Appendix F.

2.2 Cluster-Level Analysis Methods

For the cluster-level analysis, we assume that the number of patients in cluster/FP i (i=1 to 28) with BP controlled and the total number of patients in the cluster/FP are denoted by r_i and n_i, respectively. For FP i, the log odds of number of patients with BP controlled is estimated as

$$\log odd_i = \log\left(\frac{r_i}{n_i - r_i}\right),$$

and its variance is

$$\text{var}_i = \frac{1}{r_i} + \frac{1}{n_i - r_i}.$$

2.2.1 Un-weighted Regression

Comparison to the standard multiple linear regression: log odd$_i$ = $\beta x_i + u_i$, in which the vector of regression coefficients β represents differences in the log odds of the number of patient with BP controlled corresponding to the effects of the covariates x, the un-weighted regression methods [19, 20] assume the cluster-level random effects u_i follow normal distribution with mean zero and constant variance σ^2. In this method, each cluster/FP is given equal weight, which does not allow for the differing precision with which the log odds is estimated in each FP.

2.2.2 Weighted Regression

The weighted regression method [19,20] uses the same model as the unweighted regression method above, i.e. $\log \text{odd}_i = \beta x_i + u_i$. However, when obtaining the estimate of coefficient β, it allocates different weights to each cluster/FP. The weight for each cluster/FP is defined as $w_i = 1/\text{var}_i$ for FP i. Therefore, FP with smaller variance, i.e. greater precision, will have larger influence on the estimated regression coefficients. This model assumes that the variance of the log odds in each FP is $\text{var}_i \times \phi$, where ϕ is the over-dispersion parameter.

2.2.3 Random-Effect Meta-Regression

If we assume that the data from each paired cluster are arising from a meta-analysis of independent randomized controlled clinical trials, then we can apply the traditional random effect meta-analytic method to pool the results from all the pairs [24, 25]. The random-effect meta-regression method for analysing cluster randomized trial consists of two steps. First, the treatment effect is estimated for each paired clusters. Second, the overall treatment estimator is calculated as a weighted average of the paired clusters estimates, where weights equals to the inverse of the estimated variances of treatment effects of the paired clusters.

When calculating the weights of the treatment effect of the paired clusters, we considered two situations: First, without adjusting the variance with variance inflation factor (VIF), i.e. $\text{weight}_i = 1/\text{var}_i$, where weight_i is the weight assigned to the i^{th} pair of FPs. Second, with adjusting the variance with VIF, i.e. $\text{weight}_i = 1/(\text{var}_i \times \text{VIF})$, where $\text{VIF}=1+(m-1)\times \text{ICC}$, $m = 55$ is the number of patients from each FP, ICC = 0.077 is the intra-cluster correlation coefficient estimated from the CHAT data.

2.3 Individual-Level Analysis

All the individual-level analysis methods in this thesis are based on the same model — standard logistic regression model. We assume that the number of patients in cluster/FP i (i=1 to 28) with BP controlled and the total number of patients in the cluster/FP are denoted by r_i and n_i, respectively. For patient j from FP i, the standard logistic regression model is:

$$\log\frac{p(y_{ij}=1)}{1-p(y_{ij}=1)} = \beta x_{ij} + \mu_i,$$

where

$i = 1,2,\cdots,28.\ \ j = 1,2,\ldots,55;$

$u_i \sim Normal\left(0,\sigma^2\right) \quad \sigma^2 \text{ is const};$

$$p(y_{ij}=1) = \frac{r_i}{n_i};$$

x_{ij} is individual-level explanatory variables including study group assignment.

Standard logistic model assumes that data from different patients are independent. Therefore it is not valid for analyzing cluster randomized trials. However, the following statistical methods extend the standard logistic methods by adding particular strategies to handle the clustering of the data, and therefore are valid for analyzing clustering data.

2.3.1 Robust Standard Error

Compare to the standard logistic regression, the robust standard error method [19, 26] gives the same estimates since both of them assume independent data to get the estimate of the treatment effect. However, in the robust standard errors method, the standard errors for all the estimates are adjusted to allow for clustering of the data, while the standard logistic regression still assumes independent data to calculate the standard errors. The 'robust' standard errors are calculated using the 'sandwich' variance estimator.

2.3.2 Generalized Estimating Equations

Generalized estimating equations (GEE) [19, 27, 28] extend the standard logistic regression model to allow for clustering. This is achieved by specifying a correlation matrix that describes the association between different individuals in the same cluster. For cluster randomized trial, it is assumed that all correlations between

different individuals in the same cluster are the same, i.e. the correlation matrix is exchangeable.

2.3.3 Random Effect Logistic Regression

Compared to the standard logistic regression, the random effect logistic regression method [19, 20, 25, 28] includes a cluster-level random effect in the model and assumes this random effect follows normal distribution with zero mean and unknown variance τ^2 (the between cluster variance); τ^2 is estimated in the regression.

2.3.4 Bayesian Random Effect Regression

Compared to the classical random effect logistic regression, in the Bayesian random effect regression model [29], we assume the random effect follows a normal distribution with zero mean and unknown variance τ^2. The uncertainty of τ^2 is taken into account by assuming a prior distribution which presents the researcher's pre-belief or external information to τ^2. The observed data are presented as a likelihood function, which is used to update the researcher's pre-belief and then obtain the final results. The final results are presented as the posterior distribution. For binary outcomes, we obtain the log odds ratio of the treatment effect directly from the posterior distribution. The log odds ratio can be easily transformed to odds ratio scale in which we are interested.

In our Bayesian analysis, we assume the uniform non-informative prior distribution with lower and upper bounds as 0 and 10 respectively, to minimize the influence of the researcher's pre-belief or external information on the observed data. Consequently, the result from the Bayesian approach should be comparable to the results from the classical statistical methods. We also assume that the prior distribution for all the coefficients follows a normal distribution with mean zero and variance 1.0E-6. The total number of iterations to obtain the posterior distribution for each end point is 500,000, the burned-in number is 10,000, the seed is 314159. The convergence of the Markov Chain can be evaluated from the plot of the entire posterior distributions including dynamic trace plots, times series plots, density plots and autocorrelation plots. They are provided in Appendix D. The results from the Bayesian random effect logistic regression are discussed in Chapter 3 and presented in Appendix D and Appendix E.

2.4 Sensitivity Analysis of Priors for Bayesian model

In our primary analysis using the Bayesian model, we assume the prior of the variance of the cluster-level random effect follows a uniform distribution with 0 and 10 as its lower and upper bounds, respectively. However, a sensitivity analysis is necessary to assess the robustness of this specification according to the guideline of reporting results of a randomized controlled trial from Bayesian analysis [23]. For one of the primary outcomes of the CHAT trial — BP controlled, we evaluate the influence of different priors on the estimated odds ratio of the treatment effect and its 95%

confidence interval. The non-informative priors include uniform distribution with lower bound as 0 and upper bound as 1, 5, 10, 50, and 100 respectively. We also choose the conjugate priors for the variance of the random effect. They are Inverse Gamma (0.001, 0.001), Inverse Gamma(0.01, 0.01) and Inverse Gamma (0.1, 0.1).

Chapter 3

Results

3.1 Missing Data in the CHAT Trial

Missing values was not a serious problem in the CHAT trial since the data collection was based on the chart review. There were no missing values for the primary outcomes and the secondary outcomes. The missing values about the demographic information and health conditions of the CHAT patients were very few and they were quite balanced between the intervention and control groups.

For the demographic information, there was only one missing value about the age and gender in the CHAT trial and it was in the intervention group. Since neither age nor gender was a significant covariate in predicting the primary or secondary outcomes, we did not perform any imputation for them.

For the baseline diagnostic characteristics of the CHAT patients, there were three missing values indicating if the patients had diabetes at the baseline. Two of the missing values were in the control group and the other missing value was in the intervention group. We treated these three patients as without diabetes at baseline when determing if the patient's BP was controlled or not. The missing values of baseline diagnostic characteristic such as heart disease, stroke or TIA, hypertensive medication,

hypertension, smoke status and so on, were very few. Therefore, imputations for these values were not necessary.

The detailed information about the missing data in the CHAT trial was presented at Table 1 in Appendix E.

3.2 Demographic Information and Diagnostic Characteristics

Of the 1540 patients who were cluster randomized, there were 41% (319/770) male patients in the control group and 44% (339/769) male patients in the intervention group. At the beginning of the trial, the mean age of the patients is 74.36 with standard error (SE) 6.22 and 74.16 with SE 6.14 in the control and intervention groups, respectively. The detailed demographic information of the CHAT patients is presented at Table 2 in Appendix E.

The baseline diagnostic characteristics of the CHAT patients were almost balanced between the intervention and control groups. For examples, 16% (123/768) patients in the control group and 18% (140/769) patients in the intervention group had diabetes at baseline; 25% (192/769) patients in the control group and 26% (201/767) patients in the intervention group had heart disease at baseline; 5% (41/766) and 8% (62/768) patients had stroke or TIA at baseline in the control and intervention groups, respectively. However, the percentages of patients who took anti-hypertensive medication at baseline were different between intervention and control groups. In the control group, there was only 54% (415/770) of patients who took anti-hypertensive

medication, while there were 62% (477/769) of patients who took anti-hypertensive medication in the intervention group. The details of the baseline diagnostic characteristics of the CHAT patients are summarized at Table 3 in Appendix E.

3.3 Comparison of Patients BP at Baseline and end of Trial

At baseline, the mean systolic BP of the patients in the control and intervention groups were 136.14 mmHg (SD=17.92) and 135.41 mmHg (SD=17.41), respectively. At the end of the trial, the mean systolic BP of the patients in the control and intervention group was 135.74 mmHg (SD=17.84) and 133.66 mmHg (SD=17.29), respectively. The differences of the mean systolic BP between the intervention and control group was very small at both baseline and the end of the trial. The situation of the mean diastolic BP was similar to that of the systolic BP.

In addition, there were 55% (425/770) of patients in the control group and 55% (420/77) of patients in the intervention group with controlled BP at baseline. There were 53% (409/770) of patients in the control group and 56% (434/770) of patients in the intervention group with controlled BP at the end of the trial. The percentages of patients with controlled BP in the intervention and control groups at baseline were quite similar to those at the end of the trial. The situation for the patients with controlled systolic BP was very similar to that for patients with controlled BP.

The balances of the patients' BP condition between the baseline and the end of the trial indicated that the intervention of pharmacy BP clinic linked with the FPs did

not improve the patients' BP significantly. The detailed information about the comparison of patients BP at baseline and the end of the trial is presented at Table 4 in Appendix E.

3.4 Results of Primary Analysis

In analyzing the binary primary outcomes of the CHAT trial — BP controlled, systolic BP controlled, average BP controlled, and average systolic BP controlled, we applied eight classical statistical methods and one Bayesian method. The results from different statistical methods were different. However, the estimates obtained from all of the nine methods showed that there were no significant differences in improving the patients' BP between the intervention and the control groups.

For the primary outcome "BP controlled", without adjustment for covariates, the odds ratio and 95% confidence interval for the treatment effect from the cluster-level analysis were 1.14 (0.71 1.83) for unweighted regression, 1.30 (0.87 1.93) for weighted regression, 1.09 (0.68 1.74) for random effect meta-regression without adjusting for VIF, and 1.17 (0.72 1.90) for random effect meta-regression with adjusting for VIF. The results from different methods are quite different from each other. For two of the cluster-level methods, i.e. un-weighted and weighted linear regression methods, when including 'center' as the covariate in the models, we found that 'center' was not significant at level of $\alpha = 0.05$ on predicting if the patients' BP were controlled at the end of the trial. Compared to the model without adjustment for

'center', the treatment effects were slightly different and the 95% confidence intervals for the treatment effects were narrower. When adjusting for 'center' as a covariate, the odds ratio and 95% confidence interval for the treatment effect were 1.14 (0.72 1.81) for un-weighted regression and 1.30 (0.89 1.91) for weighted regression.

For individual-level methods, without adjustment for covariates, the odds ratios and 95% confidence interval of the treatment effect were 1.14 (0.93 1.39) for standard logistic regression method, 1.14 (0.72 1.80) for robust standard error method, 1.14 (0.72 1.80) for GEE method, 1.10 (0.65 1.86) for random effect logistic regression method, and 1.09 (0.61 1.94) for Bayesian random effect logistic regression method without adjustment for any covariate. When we included some patients' baseline information as the covariates in the models, the odds ratios of the treatment effect slightly changed and the 95% confidence intervals tend to be much narrower compared to without adjustment for any covariate. The odds of the treatment effect were 1.17 (0.95 1.44) for standard logistic regression method, 1.17 (0.79 1.73) for robust standard error method, 1.15 (0.76 1.72) for GEE method, 1.13 (0.71 1.80) for random effect logistic regression method, and 1.13 (0.68 1.87) for Bayesian random effect logistic regression method. We included 'diabetes', 'heart disease' and 'BP controlled' at baseline as covariates in the models since they were all significant factors in predicting if BP controlled at the end of the trial at level of $\alpha = 0.05$. The other factors, such as age, gender, experienced stroke or TIA, retinopathy, nephropathy, PVD, aortic aneurysm and anti-hypertensive medication prescribed at baseline were not included in the models since they were not significant at level of $\alpha = 0.05$. The

results indicated that patients with diabetes at baseline were more likely to get controlled BP at the end of the trial. Also, patients without heart disease and whose BP were controlled at baseline were more likely to achieve controlled BP.

Compare the results from different statistical methods, we found that the estimates for the treatment effect from the cluster-level analysis methods are quite different, while the estimates from the individual-level analysis methods are similar. The estimate of the treatment effect from the model of random effect meta-regression with adjustment for VIF was more similar to the weighted and un-weighted linear regression models compared to the model without adjustment for VIF. In our case, adjusting the model for VIF is more appropriate since the clustering of the data was taken into account.

Among all the methods we applied, we found that the Bayesian random effect logistic regression gave the largest standard error for the estimate, while the standard logistic regression method produced the smallest standard error for the estimate. This was due to the fact that standard logistic regression model did not count the effect of clustering while the Bayesian random effect logistic regression collected all the uncertainty of the parameters. For primary outcomes — systolic BP controlled, the results were quite similar to primary outcome of if BP controlled.

Compared to the treatment effect in analysis of outcomes 'BP controlled', and 'systolic BP controlled', we found that the odds ratios in analysis of the outcome 'average BP controlled' and 'average systolic BP controlled' were closer to 1. For example, in analysis of outcome 'average BP controlled', the odds ratios and 95%

confidence intervals were 1.03 (0.63 1.69), 1.12 (0.73 1.74), 1.00 (0.60 1.67), 1.04 (0.64 1.69), 1.03 (0.84 1.26), 1.03 (0.64 1.66), 1.03 (0.64 1.66), 1.01 (0.59 1.72), 1.01 (0.57 1.80) from unweighted regression, weighted regression, random-effect meta-regression without adjustment for VIF, random-effect meta-regression with adjustment for VIF, standard logistic regression, robust standard error, GEE, random effect logistic regression and Bayesian random effect logistic regression methods respectively. This difference was due to the different definitions to the outcomes. The determination of if patients' average BP controlled was based on the average of the last three BP readings in the period between the randomization and the end of the trial, while the determination of if patients' BP controlled was based on the last BP reading within that period.

The comparison of the results from different statistical methods are discussed in detain in Chapter 4. The detailed results for primary outcomes are presented and ploted in Tables 4-7 and Figures4-11 in Appendix D and E.

3.5 Results of Secondary Analysis

Eight secondary outcomes were analyzed for the CHAT trial. They were BP monitored, the frequency of BP monitoring, average systolic BP, average diastolic BP, percent of patients with BP controlled at the end of the trial, percent of patients with systolic BP controlled at the end of the trial, difference of percent of patients with BP controlled between baseline and at the end of the trial, and the difference of percent of

patients with systolic BP controlled between baseline and at the end of the trial. The definitions of the secondary outcomes are given at Table C3 in Appendix C. The treatment was not significant for all of these secondary outcomes compared to the control at level of $\alpha = 0.05$.

For the binary outcome 'BP monitored', the odds ratio of the treatment effect and its corresponding 95% confidence interval were 1.16 (0.73 1.86) from the cluster level analysis using random effect meta-regression model, which is consistent with the result from the individual-level analysis using GEE model without adjustment for any covariate 1.15 (0.72 1.84) . When using the GEE model with adjustment for covariates, we found that patients with hypertension at last review or taking hypertensive medicine were more likely to have their BP recorded during the twelve month period of the trial compare to patients who had no hypertension at last review or were not taking anti-hypertensive medications.

For the secondary outcome 'frequency of BP monitoring', the estimate for the treatment effect and its 95% CI were 0.26 (-0.52 1.04), which indicated that the treatment did not change the frequency of BP monitoring significantly. After including baseline characteristics in the linear regression, the treatment effect was still not significant with the estimate and its 95% CI being 0.04 (-0.39 0.47). We also found that the BP for patients with hypertension at last review, nephropathy at baseline, or heart disease at baseline were more frequently monitored than the patients without those diseases. The frequency of the BP monitoring was higher for older patients compare to the younger patients. The frequency of BP monitoring for patients who

were taking hypertensive medicine tends to be higher than the patients who were not taking hypertensive medicine.

For other continuous secondary outcomes, we found that the CHAT intervention did not change the systolic BP, diastolic BP, percentage of patients with BP controlled at the end of the trial, and the percentage of patients with systolic BP controlled at the end of the trial, the difference of percentage of patients with controlled BP or controlled systolic BP between baseline and the end of the trial at significant level of $\alpha = 0.05$. The results were consistent when using different statistical methods. For example, the estimated treatment effects for the cluster-level average diastolic BP were 0.52 (-1.44 2.48) from the weighted linear regression model, 0.35 (-1.65 2.35) from two sample T-test, and 0.31 (-1.75 2.37) and 0.08 (-2.06 2.22) from random effect meta-regression model without and with adjustment for VIF respectively. The result from Wilcoxon rank sum test, a nonparametric method, also indicated non-significance of the treatment effect at level of $\alpha = 0.05$. The detail results for secondary outcomes were presented at Table 9 in Appendix E.

3.6 Impact of Priors for Bayesian Analysis

To verify the robustness of the results from Bayesian random effect logistic regression, we evaluated the impact of different prior distributions of the variance parameter for the cluster-level random effect in analysis of a primary outcome, BP

controlled, without adjustment for any covariates. We chose non-informative priors including uniform(0, 1), uniform(0, 5), uniform(0, 10), uniform(0, 50), uniform(0, 100), Inverse Gamma(0.001, 0.001), Inverse Gamma(0.01, 0.01) and Inverse Gamma(0.1, 0.1). The Inverse Gamma prior is also the conjugate prior for the variance parameter. The odds ratios and 95% CIs were 1.11 (0.64 1.92), 1.09 (0.61 1.94), 1.09 (0.61 1.94), 1.09 (0.61 1.94), 1.09 (0.61 1.94), 1.11 (0.63 1.94), 1.11 (0.63 1.95), 1.12 (0.64 1.95) correspondingly. We found that results were quite consistent when using different priors. For non-informative priors, the estimates and the 95% CIs were almost the same when the upper bound of the uniform distribution was greater than or equal to 5, which implied that 1 might not be a big enough upper bound for the uniform prior in our case. The results of this comparison were presented at Table 10 in Appendix E.

Chapter 4

Discussion

4.1 Summary of Key Findings

In this thesis, we applied four cluster-level summary statistics and five individual-level analysis [see Chapter 2]. Only one method, individual-level standard logistic regression, is invalid because it fails to account for the between-cluster variation. Ignoring the clustering of the data leads to underestimate the standard error for the treatment effect. Therefore, standard logistic regression tends to overestimate the treatment effect if being used to analyze the clustering data. Each of the other methods handled clustering by certain techniques, and would therefore be appropriate.

All of the statistical methods are based on the same underlying model — logistic regression. However, their parameter estimates and especially their standard errors differed due to different strategies to deal with the clustering of the data. The parameter estimates from the cluster-level analyses are quite variable. However, since the standard errors varied correspondingly, the *P*-values are more consistent. Results from random- effect meta-regression with adjustment for VIF were more comparable to the un-weighted than the weighted regression. In our case, including the adjustment for

VIF for the meta-regression model yielded more consistent results with other cluster-level statistical methods.

For individual-level methods, the log odds ratios were identical for standard logistic regression method and robust standard errors method because both of the methods obtained their estimates by assuming independence of the data. However, robust standard error method adjusts its standard errors using "sandwich" variance estimator by allowing for clustering.

Both with and without adjustment for covariates, odds ratios from classical random effect logistic regression and Bayesian random effect logistic regression were similar. However, the confidence interval from Bayesian logistic random effect model was much wider than the confidence intervals from other methods since Bayesian approach incorporates all kinds of variability. The point estimates, standard errors and hypothesis tests for the classical methods are based on the assumption of infinite but identical repetitions on the fixed unknown parameters. This process is deductive and the estimates of parameters are summarized from the observations directly. Compared with these classical methods, Bayesian method treats all of the unknown parameters as random variables.

In Bayesian analysis, the researcher's subjective pre-beliefs are expressed as prior distribution functions. Even though these beliefs can be updated by the likelihood function of the observed data, misspecification of priors has some impact on the posterior in some cases. In our sensitivity analysis of the Bayesian random effect logistic regression model, we assumed that the variance of the cluster-level random

effect follows normal distribution with mean zero and variance τ^2. The commonly used priors for the variance parameter are uniform and inverse gamma [30]. When assuming a uniform prior distribution, we find that the results become stable when the upper bound of the uniform prior is at least 5. We also find that the results are sensitive to the parameter ε when assuming prior distribution as inverse gamma(ε, ε). As pointed out by Gelman [30], when τ^2 is estimated to be close to zero, the results are sensitive to the parameter ε. It convinces us that the uniform(0, 10) distribution is a proper non-informative prior for our analysis.

In the analysis of cluster randomized controlled trials, adjusting for important covariates correlated with outcome was able to increase the precision in analysis. By adjusting for important covariates, we were able to control for the effect of imbalances in baseline risk factors and reduce the unexplained variation.

In summary, the key statistical findings can be summarized as:

1) All but weighted regression method yield similar point estimates of the treatment effect. This is not surprising since weighted regression method can potentially affect the location of the estimate as well as the precision.
2) The random effect meta-regression method yields different estimates with or

   without adjustment for VIF. Adjusting for VIF is more appropriate in the analysis of cluster randomized trials.
3) Ignoring the clustering yields a narrower confidence interval, but this is not correct.

4) The Bayesian method yields widest confidence interval.

5) Adjusting for significant covariates increases the precision in the analysis of cluster randomized trials.

The above statistical findings from our study are comparable with findings from another study [31].

4.2 How the Findings Compare With Results from Other Studies

According to our literature search, several randomized controlled trials were relevant to the CHAT study in terms of the intervention and outcome.

Results from Syme's study [12] of people with high BP indicated that BP was most likely to be controlled among patients receiving visits from community health workers. The community health workers provided the information about hypertension and discussed family difficulties, financial strain, and employment opportunities. They also provided support and assistance when appropriate.

The study by Nessman *et al.* [13] improved the Freire's theory that individualized the information to the subjects' problems is the most effective educational material. This approach was translated into a management program for high BP aimed at empowering patients to learn enough about high BP so that they could monitor their disease and select their own drugs for treatment. Compared with control patients, intervention patients had significantly lower diastolic BPs.

In the study by Zarnke *et al.* [14], they found that patient-directed management of high BP resulted in a significant, favourable change in mean BP, compared to office-based care.

In the systematic review by Fahey *et al.* [11] on interventions used to improve control of the blood pressure in patients with hypertension, their results show that educational interventions themselves seem unlikely to improve the BP of patients, and the health professional led care might associate with the improved blood pressure control.

From our analysis, the CHAT intervention — community based BP management program, does not improve the BP of patients significantly. Comparing our results with the other studies mentioned above and the similar studies reviewed by Fahey *et al.*, we found that the difference between the result from the CHAT study and other studies may be due to the difference in designing trials. First, the target population of the CHAT study is the older adults at least 65 years old. However, all the other studies have strict inclusion and exclusion criteria, and focus on only the patients with hypertension. Second, all of the other studies are relatively small trials compared with the CHAT study. In the CHAT trial, there are 1540 patients participating the study. However, there are less than hundred participants in most of the other trials. For example, in Nessman's study, the participants were only 52 previously noncompliant hypertensive patients. Third the multi-faceted intervention of the CHAT trial is similar to but not exactly the same as the interventions of the other studies. In addition, the intensiveness and duration of the interventions differ markedly between the CHAT trial

and the other studies. For example, in Zarnke's study, 31 patients who had chronic stable essential hypertension without secondary causes or unstable cardiovascular disease were selected from 11 family physicians' office and a tertiary care hypertension research unit. Patients were randomly assigned (2:1 ratio) to either a patient-directed management strategy using home blood pressure monitoring to adjust drug therapy if readings consistently exceeded defined limits, or office-based management through physician visits. The duration of the intervention is only 8 weeks. All of the above differences between the CHAT study and other studies might lead to differences in results.

4.3 Limitations of the CHAT Study

The CHAT trial is a pragmatic trial. Compared to the explanatory trials which are designed to find out the efficacy of a treatment under ideal, experimental conditions, pragmatic trials are designed to evaluate the benefits of an intervention in normal clinical or routine care settings [29], which is exactly the objective of the CHAT trial. The pragmatic trial has high external validity and relevance on practice [32]. In addition, the multi-faceted intervention of the CHAT trial emphasizing community pharmacy BP clinics linked with FPs comprise a number of separate elements which seem essential to the proper functioning of the intervention although the 'active ingredient' of the intervention that is effective is difficult to specify. In the CHAT trial,

we attempted to operate BP management guidelines and we found no evidence of harm created by the intervention.

Though we exerted all the strength of multi-faceted intervention and the pragmatic trial, we are still limited by some design issues.

The first design limitation is about the sample size. From each of the 28 FPs, we randomly sample 55 patients, which is relatively small. Some patients in the intervention group may not comply with the intervention, which leads to underestimate the treatment effect.

The second design limitation is that the type of the intervention in CHAT study may not be intensive and long enough for the behavior change of the patients. Community pharmacy BP clinics help older adults to learn more about hypertension so that they can take a more active role in monitoring their BP and better understand their own risk profile. These features of the intervention are hypothesized to translate into improved patients' awareness and adherence to BP self-care, and therefore improve their BP. According to Icek Aizen [33], a long term and intensive communication with the patients is necessary to change their attitudes or behaviors. And moreover, the benefits from the change of attitude or behavior, such as the improvement of BP in our study, can only be observed or detected after persisting in the new attitude or life style for a long time.

Finally, the multi-faceted intervention of the CHAT trial is a complex intervention. It consists of several separate elements which seem essential to make the intervention function properly. However, it also causes difficulties to the evaluation. In

this complex intervention, each element may be an important contribution to the effectiveness of the community pharmacy BP clinics. For example, the peer health educator in the CHAT study is one potentially complex contribution in a large and complex combination of diverse health professionals' expertise, medications, organizational arrangements and treatment protocols that constitute the intervention [34].

4.4 Clinical Implications of Results

This trial evaluated the effectiveness of the community-based BP monitoring program in improvement of the BP for older patients. According to our analysis results, it does not significantly improve the patients' BP in terms of increasing the number of patients with BP controlled, decreasing the systolic or diastolic BP and increasing the frequency of BP monitoring in the intervention compared to those in the control group. However, this process may improve the diagnostic accuracy, health profession adherence, patient adherence to self-care recommendations, and coverage. In addition, this process has the potential to improve the cardiovascular health of older adults by providing convenient, reliable BP monitoring and enhancing knowledge and communication among providers and patients. Moreover, patient education and self-monitoring can reduce physicians' time spent on following low-risk patients, identify high-risk patients earlier and use resources more efficiently. Further investigation in this direction may get fruitful results.

Although the results are not positive, the CHAT study also provides a feasibility to create a multi-faceted community-based solution to manage the BP -- the Cardiovascular Health Awareness Program (CHAP) [35]. The program will help to identify and monitor senior patients who are at risk for cardiovascular disease and stroke by adequate treatment and follow-up from the appropriate health professionals.

4.5 Usefulness of Performing Sensitivity Analysis and Simulation Study

Sensitivity analysis is used to determine how sensitive a model is to changes in the value of the parameters and to changes in the structure of the model. For a cluster randomized control trial, several sensitivity analyses can be considered.

First, a variety of statistical methods for the binary outcomes have been proposed. However, there are very few methodological studies that provide guidance on determining which method is the best. In practice, these different results might cause confusion. Therefore, comparing the results from different methods might help researchers to draw a safer conclusion.

Second, sensitivity analysis can be used to investigate the sensitivity of the conclusions to different model assumptions. For example, in the random-effects model, we assume that the cluster-level random effect follows a normal distribution on the log odds scale. However, a sensitivity analysis can be carried out by allowing empirical investigation on the distribution of the random effects. In addition, a sensitivity analysis

can also indicate which parameter values are reasonable to use in the model. For example, in our Bayesian random effect logistic regression model, the impact of different prior distributions of the variance of the random effect is investigated. A proper prior is specified based on the comparison of the results from different prior assumptions.

Finally, a sensitivity analysis can be performed to compare the results from different methods by allowing the degree of clustering to vary. In other words, we can investigate the changing behavior of the results from different methods given the intra-cluster correlation coefficient changing from 0 to 1.

To compare statistical power of different statistical methods under different situations, extensive simulations are required. Recently, a simulation study by Austin [36] suggests that the statistical power of GEE is the highest among t-test, Wilcoxon rank sum test, permutation test, adjusted chi-square test, logistic random effects model and GEE given different ICC, number of clusters, and average number of patients in each cluster. Some of the statistical methods used in this thesis are not included in this simulation study.

Chapter 5

Conclusions

For the primary outcomes of the CHAT trial, our analysis results from both classical and Bayesian methods indicate that the treatment of community-based BP care program does not make significant difference in improving the BP of patients compared to the usual care at the FP's office. For the secondary outcomes of the CHAT trial, our analysis results show that the treatment does not significantly decrease the mean systolic and diastolic BP of patients, does not increase the proportion of patients who achieves controlled BP, does not significantly increase the frequency of the BP monitoring of the patients. This might be due to the limitations of the study design such as the length of the study might be not long enough and the intervention might be not intensive enough to achieve the behaviour change of the patients. However, the CHAT trial provides an evidence for the feasibility of community-based solution to manage the BP of the patients.

Theoretically, all the methods discussed in this thesis are valid methods for the analysis of cluster randomized controlled trials with binary outcomes except for the standard logistic regression model. The standard logistic regression method does not take into account the clustering of the data, while all the other methods handle the clustering of the data with their particular strategies. Therefore, the standard logistic

regression tends to underestimate the standard error of the treatment effect and its *p*-value. Correspondingly, this method might exaggerate the treatment effect.

According to our results in the analysis of primary outcomes of the CHAT trial, using different statistical models, or including baseline or diagnostic factors as covariates in the model can make the estimate of the treatment effect and its standard error different. The variability of the results from cluster-level statistical methods is quite large. The results from the individual-level statistical methods are similar.

The difference between the results from cluster-level random-effect meta-regression with adjustment for VIF and without adjustment for VIF is very large. The results from the random effect meta regression with adjustment for VIF are more consistent with the results from the un-weighted linear regression and weighted linear regression. We conclude that adjusting for VIF in the random-effect meta-regression is more proper than without adjusting for VIF. Many studies do not take into account the impact of VIF when analysing correlated data. This may be acceptable in some cases when the homogeneity of the outcome within each cluster is not very strong. However, in trials like the CHAT, patients from the same cluster/FP are more similar than patients from other FPs in terms of social and economic status, living regions and health care services they get. Therefore, it is necessary to include the impact from VIF in the model to assess the effectiveness of the treatment effect.

Among all the statistical methods, Bayesian analysis gives us the largest standard error for the treatment effect and the widest 95% CI correspondingly since the Bayesian analysis captures all kinds of variability and therefore provides more

conservative evidence to the readers. The robustness of the results from Bayesian analysis can be verified if it is consistent with the results obtained from using different prior distributions and consistent with the results from classical statistical methods as well.

Since different statistical methods, including covariates or without covariates in the models, give different results, we may suspect that different conclusions might be made when choosing different methods or adding significant covariates in the model. From the results in this study, we can not conclude which method is superior in the analysis of the cluster randomized control trial with binary outcome. Methodological studies are few to provide guidance on determining which method is the best. Simulation study including all of valid statistical methods under all kinds of situations is required.

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Appendix A:

Definitions

Table A1. Summary of Definitions

Index	Definition
A1	**Blood Pressure at Baseline** • The last BP reading before the randomization date. • Not available if there is no BP reading before the randomization date.
A2	**Average Blood Pressure at baseline** • The average of the last three BP readings if there are 3 or more than 3 BP readings before the randomization date. • The average of the last two BP readings if there are only 2 BP readings before the randomization date. • The last BP readings if there is only 1 BP reading before the randomization date. • Not available if there is no BP reading before the randomization date.
A3	**Blood Pressure at The End of Trial** • The last BP reading during the period from the beginning of the randomization date to 12 months after the randomization date. • Not available if there is no BP reading during the period from the beginning of the randomization date to 12 months after the randomization date.
A4	**Average Blood Pressure at The End of Trial** • The average of the last three BP readings if there are 3 or more than 3 BP readings during the period from the beginning of the randomization date to 12 months after the randomization date. • The average of the last two BP readings if there are only 2 BP readings during the period from the beginning of the randomization date to 12 months after the randomization date. • The last BP reading if there is only 1 BP reading during the period from the beginning of the randomization date to 12 months after the randomization date. • Not available if there is no BP reading during the period from the beginning of the randomization date to 12 months after the randomization date.
A5	**Systolic Blood Pressure at Baseline** • The last systolic BP reading before the randomization date. • Not available if there is no systolic BP reading before the randomization date.

Table A1. Summary of Definitions (Continued)

Index	Definition
A6	**Average Systolic Blood Pressure at Baseline** • The average of the last three systolic BP readings if there are 3 or more than 3 systolic BP readings before the randomization date. • The average of the last two systolic BP readings if there are only 2 systolic BP readings before the randomization date. • The last systolic BP readings if there is only 1 systolic BP reading before the randomization date. • Not available if there is no systolic BP reading before the randomization date.
A7	**Systolic Blood Pressure at End of Trial** • The last systolic BP reading during the period from the beginning of the randomization date to 12 months after the randomization date. • Not available if there is no systolic BP reading during the period from the beginning of the randomization date to 12 months after the randomization date.
A8	**Average Systolic Blood Pressure at End of Trial** • The average of the last three systolic BP readings if there are 3 or more than 3 systolic BP readings during the period from the beginning of the randomization date to 12 months after the randomization date. • The average of the last two systolic BP readings if there are only 2 systolic BP readings during the period from the beginning of the randomization date to 12 months after the randomization date. • The last systolic BP reading if there is only 1 systolic BP reading during the period from the beginning of the randomization date to 12 months after the randomization date. • Not available if there is no systolic BP reading during the period from the beginning of the randomization date to 12 months after the randomization date.
A9	**(Average) BP controlled** • If the (average) BP reading is available and the (average) systolic BP<=140 and (average) diastolic BP<=90 for patients without diabetes or target organ damage. • If the (average) BP reading is available and the (average) systolic BP<=130 and (average) diastolic BP<=80 for patients with diabetes or target organ damage.
A10	**(Average) Systolic BP Controlled** • If the (average) systolic BP reading is available and the (average) systolic BP<=140 for patients without diabetes or target organ damage. • If the (average) systolic BP reading is available and the (average) systolic BP<=130 for patients with diabetes or target organ damage.

Appendix B

Primary Outcomes

Table B1. Summary of Primary Outcomes

Index	Type	Definition
B1	Binary	**BP Controlled at End of Trial** [see *Definition A3* and *A9*] • 1 if the BP at 12 month after baseline is controlled no matter the BP at the baseline is controlled, not controlled or not available. • 0 if the BP at 12 month after baseline is not controlled or not available no matter the BP at the baseline is controlled, not controlled or not available.
B2	Binary	**Systolic BP Controlled at End of Trial** [see *Definition A7* and *A10*] • 1 if the systolic BP at 12 month after baseline is controlled no matter the systolic BP at the baseline is controlled, not controlled or not available. • 0 if the systolic BP at 12 month after baseline is not controlled or not available no matter the systolic BP at the baseline is controlled, not controlled or not available.
B3	Binary	**Average BP Controlled** [see *Definition A4* and *A9*] • 1 if the average BP at 12 month after baseline is controlled no matter the average BP at the baseline is controlled, not controlled or not available. • 0 if the average BP at 12 month after baseline is not controlled or not available no matter the average BP at the baseline is controlled, not controlled or not available.
B4	Binary	**Average Systolic BP Controlled** [see *Definition A8* and *A10*] • 1 if the average systolic BP at 12 month after baseline is controlled no matter the average systolic BP at the baseline is controlled, not controlled or not available. • 0 if the average systolic BP at 12 month after baseline is not controlled or not available no matter the systolic BP at the baseline is controlled, not controlled or not available.

Note: The *definitions* were presented at Table A1 in Appendix A.

Appendix C

Secondary Outcomes

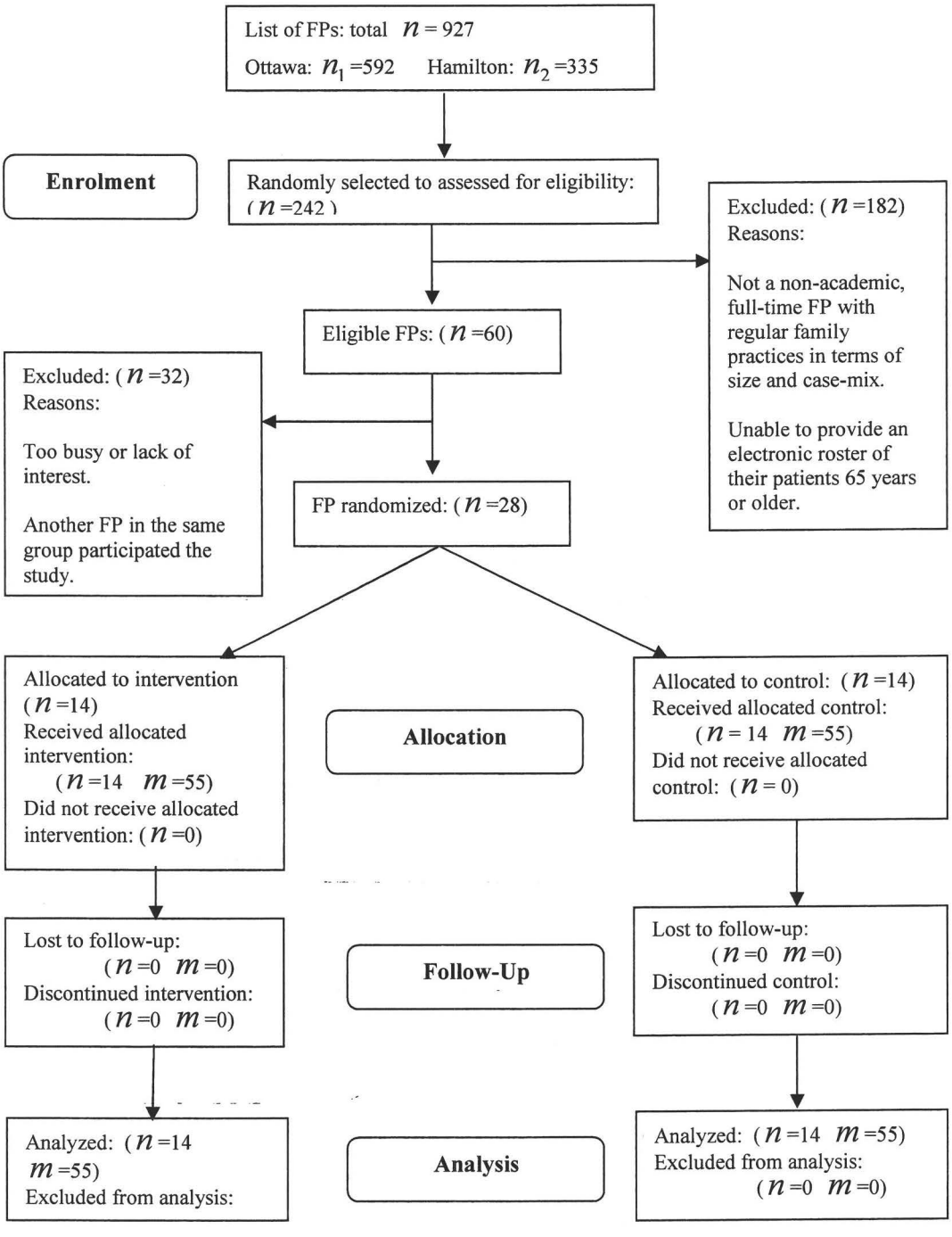
Table C1. Summary of Secondary Outcomes

Index	Type	Definition
C1	Binary	**If BP monitored** • 1 if there is at least one BP reading recorded in the last 12 month. • 0 if there is no BP reading recorded in the last 12 month.
C2	Count	**Frequency of BP monitoring** Total number of BP readings recorded in the last 12 month.
C3	Continuous	**Average Systolic BP** Average systolic BP of each practice.
C4	Continuous	**Average Diastolic BP** Average diastolic BP of each practice.
C5	Continuous	**Percent of Patient with BP Controlled at End of Trial** Percent of patient with BP controlled at 12 months after the randomization date (i.e. at the end of the trial) in the intervention compared to the control practices.
C6	Continuous	**Percent of Patient with Systolic BP Controlled at End of Trial** Percent of patient with BP controlled at 12 months after the randomization date (i.e. at the end of the trial) in the intervention compared to the control practices.
C7	Continuous	**Difference of Percent of Patients with BP Controlled Between Baseline and End of Trial** Difference of the percent of patient with BP controlled between the end of the trial and the baseline in the intervention compared to the control practices.
C8	Continuous	**Difference of Percent of Patients with Systolic BP Controlled Between Baseline and End of Trial** Difference of percent of patient with systolic BP controlled between the end of the trial and the baseline in the intervention compared to the control practices.

Appendix D

Figures

Figure 1 The Progress of Clusters and Individuals Through The Phases of The CHAT Trial



Note: n = the number of family physicians (FP)
m = the number of patients per FP

Figure 2 Graph depictions of interventions in the CHAT trial

Time Line	Intervention	Control
Pre-randomization	a	
Randomization		
Baseline (time 0)		
During 1 year from baseline	b c d e f g h	h
1 year (end of the trial)	Measurement of outcome 1) BP controlled; 2) BP monitored; 3) Frequency of BP monitoring; 4) mean systolic and diastolic BP; 5) Percentage of patients with BP controlled; etc.	

BP = Blood Pressure;

FP = Family Practice;

BP controlled if

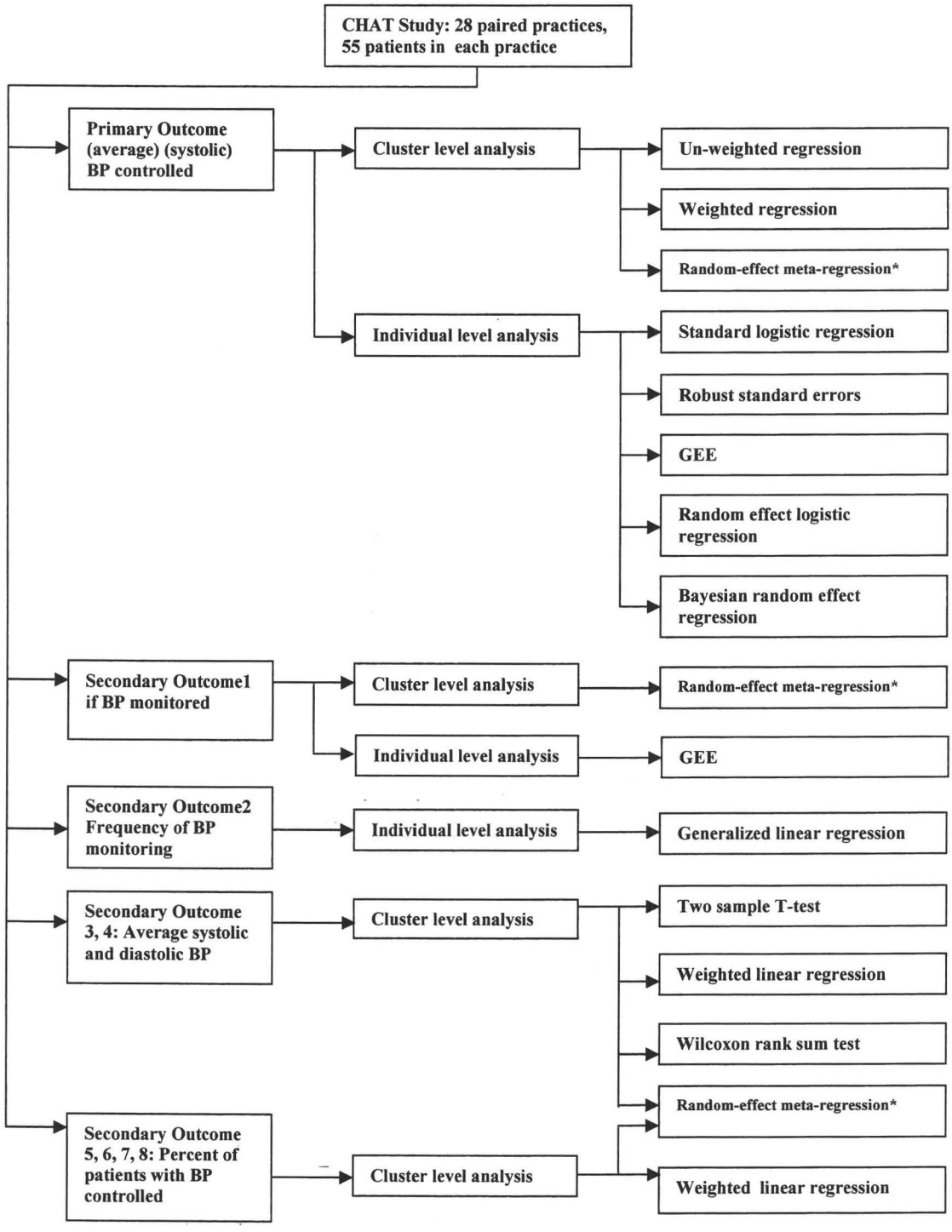
the BP reading is available and systolic BP $\leq$ 140 mmHg and diastolic BP $\leq$ 90 for patient without diabetes or target organ damage;

the BP reading is available and systolic BP $\leq$ 130 mmHg and diastolic BP $\leq$ 80 for patient with diabetes or target organ damage;

Figure 2 Graph depictions of interventions in the CHAT trial (continued)

a	Research nurses, assisted by the FP office staff, conduct the baseline audits of health records of all eligible patients 65 years and over in each practice.
b	FPs invite patients to BP clinic in pharmacy by letters
c	Standardized training of peer health educators
d	Organizing BP clinics collaborating with pharmacists: 1. Use of BPM-100 and in-store BP devices for taking BP 2. Peer health educator will review cardiovascular risk factors with patients using a standardized approach 3. Peer health educator will distribute educational materials to patients developed by the Heart and Stroke Foundation of Ontario
e	Faxing patient's BP readings and cardiovascular risk factors to FPs
f	Pharmacists provide education, monitoring, and follow up for patients who has high BP readings at the BP clinic
g	FPs and pharmacists will receive a one-page summary of the Canadian hypertension guidelines
h	Usual care at FPs' office

Figure 3. Schema of Study Analysis



* We applied the random-effect meta-regression model with and without adjustment for the Variance Inflation Factor (VIF)

Figure 4. Forest Plot: BP Controlled Without Adjustment for Covariates

Methods	OR	95% CI
Cluster Level		
Un-weighted Reg.	1.14	(0.71 1.83)
Weighted Reg.	1.30	(0.87 1.93)
Random Effect Meta Reg. (1)	1.09	(0.68 1.74)
Random Effect Meta Reg. (2)	1.17	(0.72 1.90)
Individual Level		
Standard Logistic Reg.	1.14	(0.93 1.39)
Robust Standard Errors	1.14	(0.72 1.80)
GEE	1.14	(0.72 1.80)
Random Effect Logistic Reg.	1.10	(0.65 1.86)
Bayesian Analysis	1.09	(0.61 1.94)

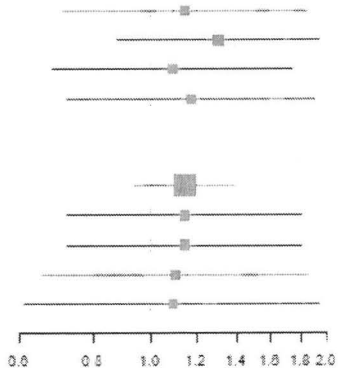


Figure 5. Forest Plot: BP Controlled With Adjustment for Covariates

Methods	OR	95% CI
Cluster Level		
Un-weighted Reg.	1.14	(0.72 1.81)
Weighted Reg.	1.30	(0.89 1.91)
Individual Level		
Standard Logistic Reg.	1.17	(0.95 1.44)
Robust Standard Errors	1.17	(0.79 1.73)
GEE	1.15	(0.76 1.72)
Random Effect Logistic Reg.	1.13	(0.71 1.80)
Bayesian Analysis	1.13	(0.68 1.87)

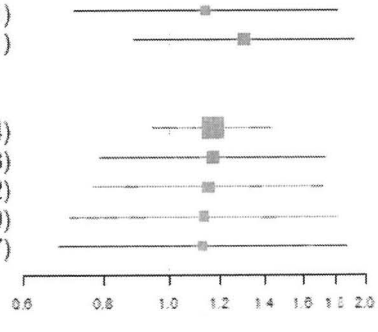


Figure 6. Forest Plot: Systolic BP Controlled Without Adjustment for Covariates

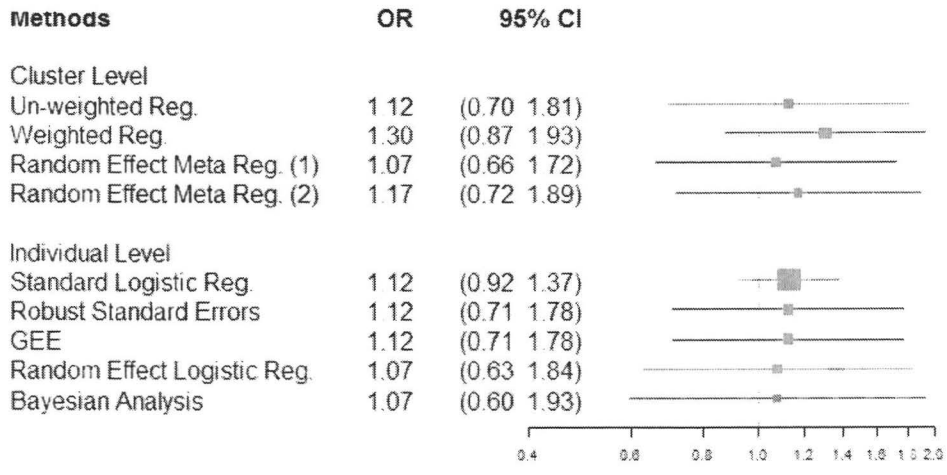


Figure 7. Forest Plot: Systolic BP Controlled With Adjustment for Covariates

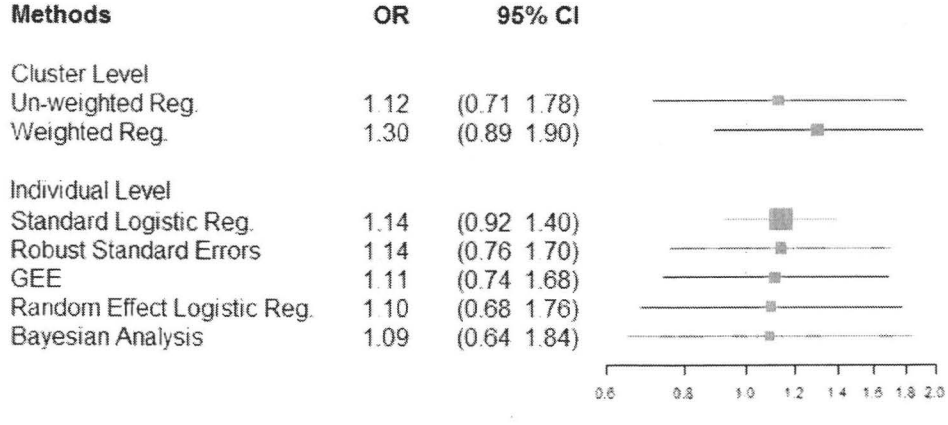


Figure 8. Forest Plot: Average BP Controlled Without Adjustment for Covariates

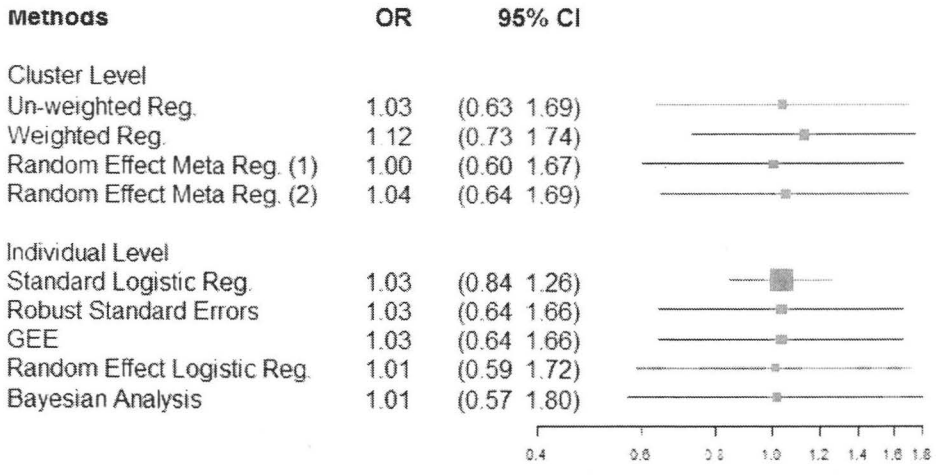


Figure 9. Forest Plot: Average BP Controlled With Adjustment for Covariates

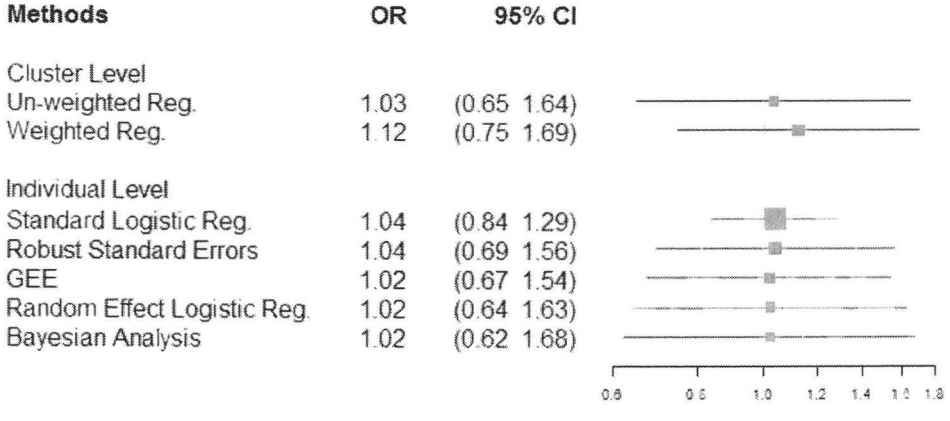


Figure 10. Forest Plot: Average Systolic BP Controlled Without Adjustment for Covariates

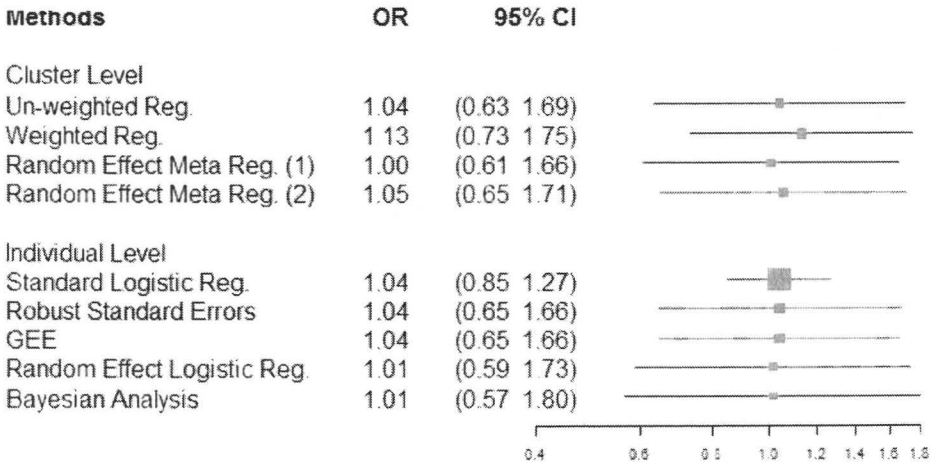


Figure 11. Forest Plot: Average Systolic BP Controlled With Adjustment for Covariates

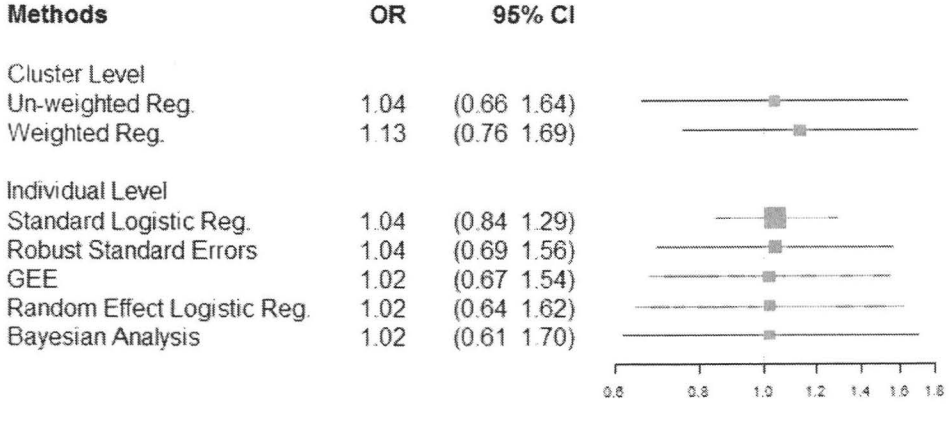
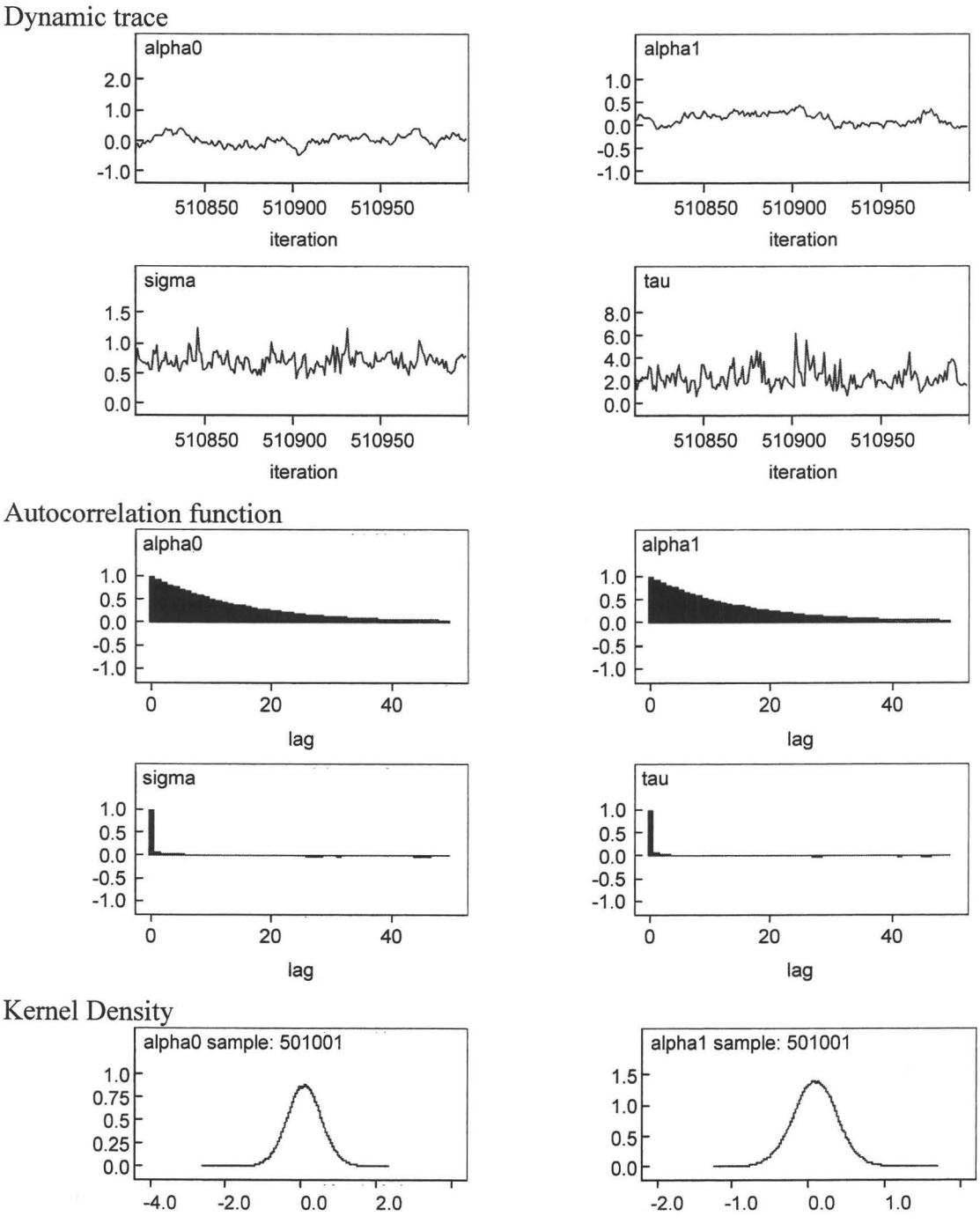
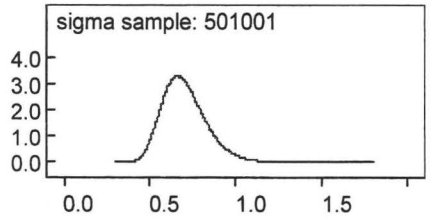


Figure 12. Diagnosis Plot for Bayesian Analysis — BP Controlled (without covariates)

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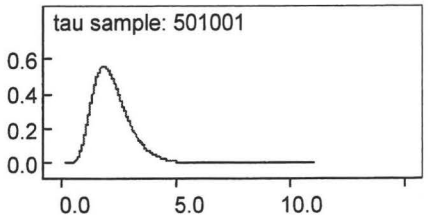
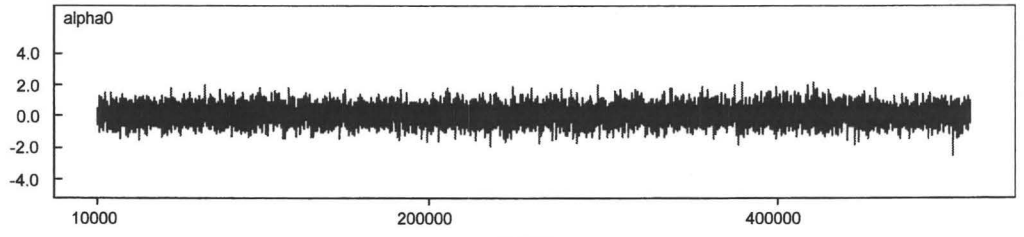
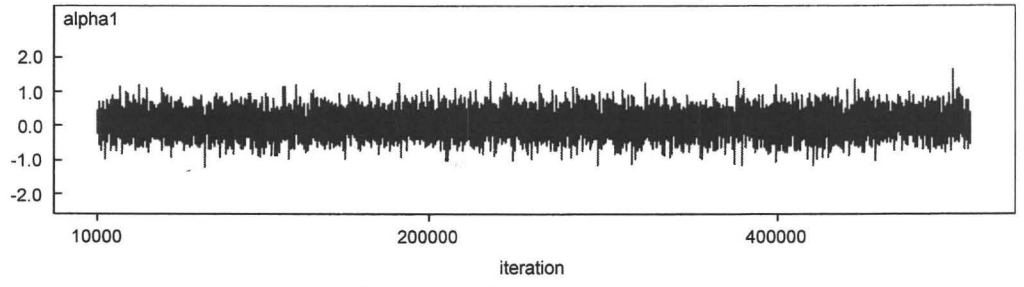
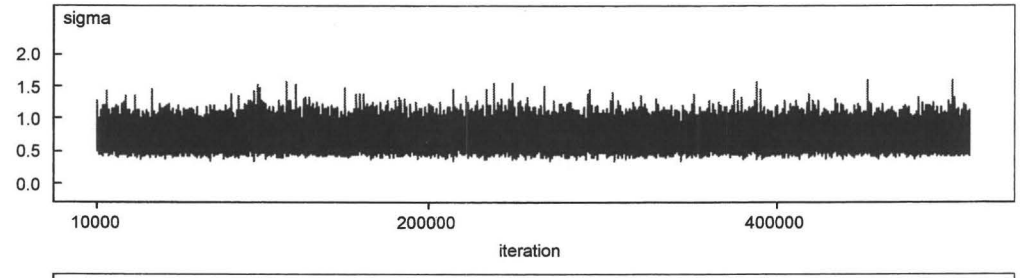
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5


tau sample: 501001
0.6
0.4
0.2
0.0
0.0
5.0
10.0

Time series


alpha0
4.0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
2.0
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


sigma
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration

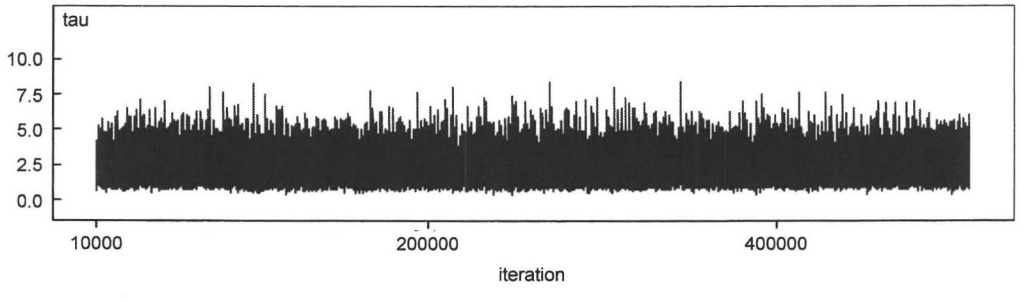
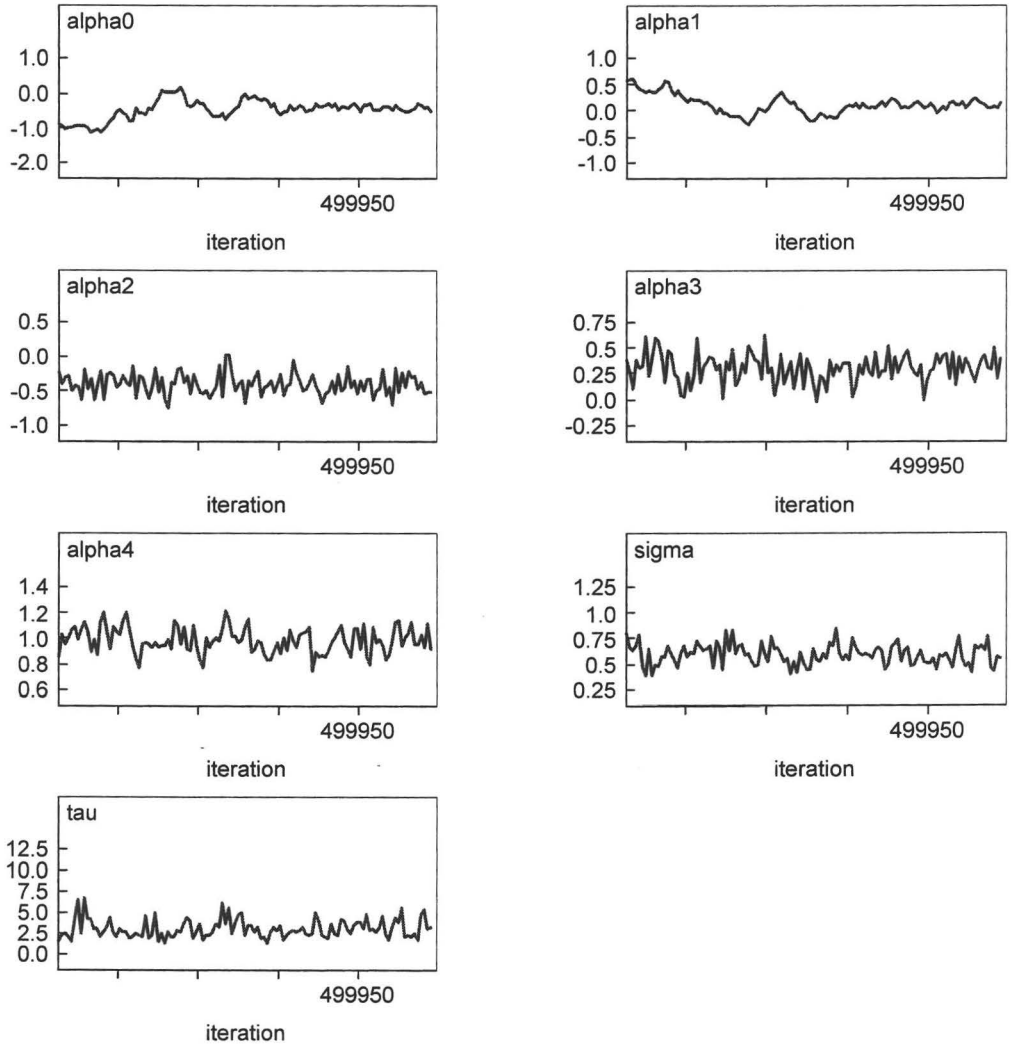
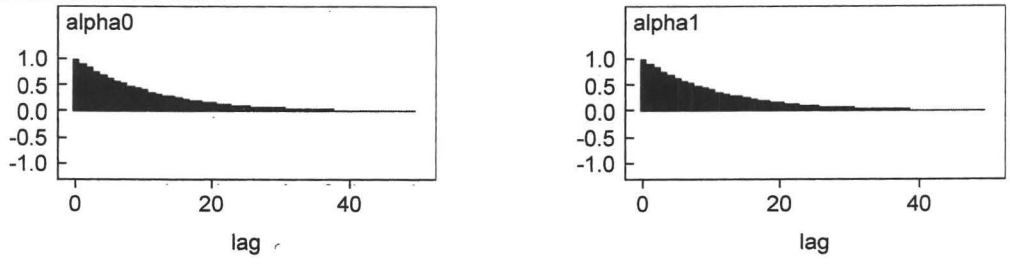

tau
10.0
7.5
5.0
2.5
0.0
10000
200000
400000
iteration

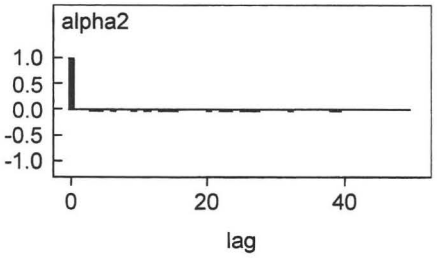
Figure 13. Diagnosis Plot for Bayesian Analysis — BP Controlled (with covariates)

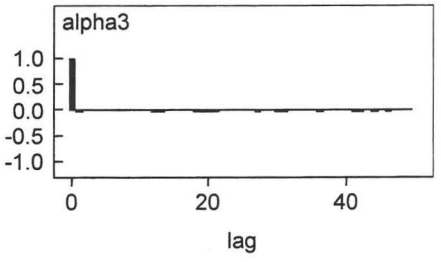
Dynamic trace

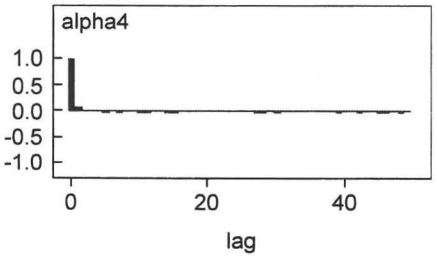


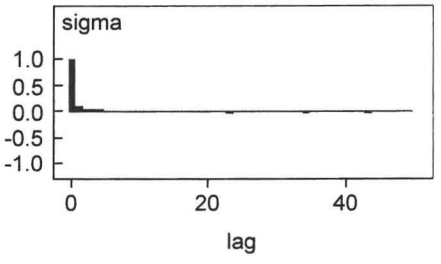
Autocorrelation function

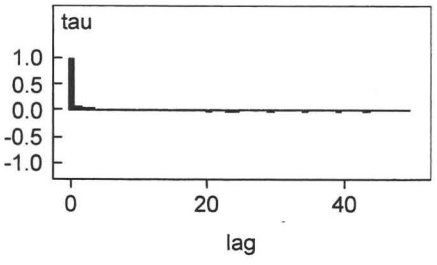




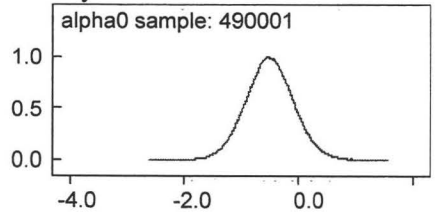


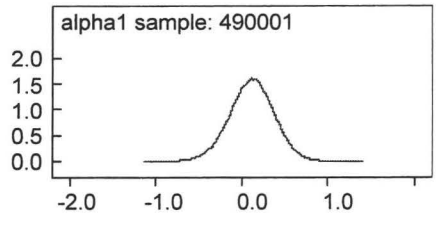


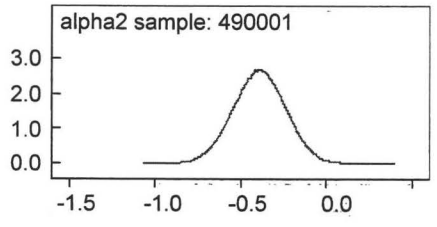


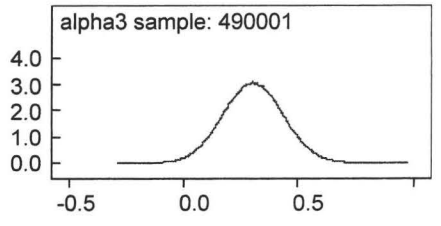


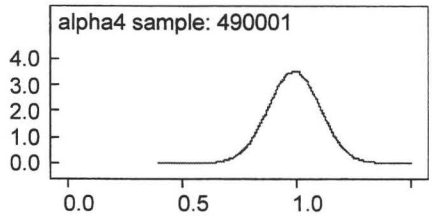
Kernel Density







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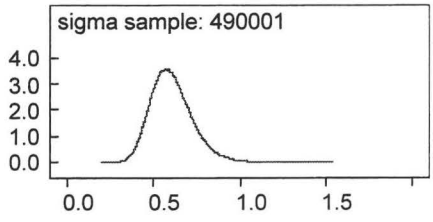
2.0
1.0
0.0
0.0
0.5
1.0


sigma sample: 490001
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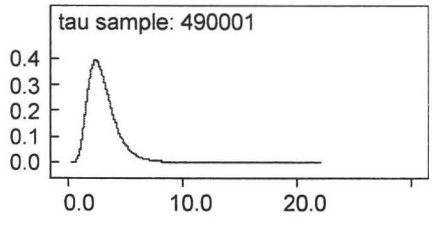
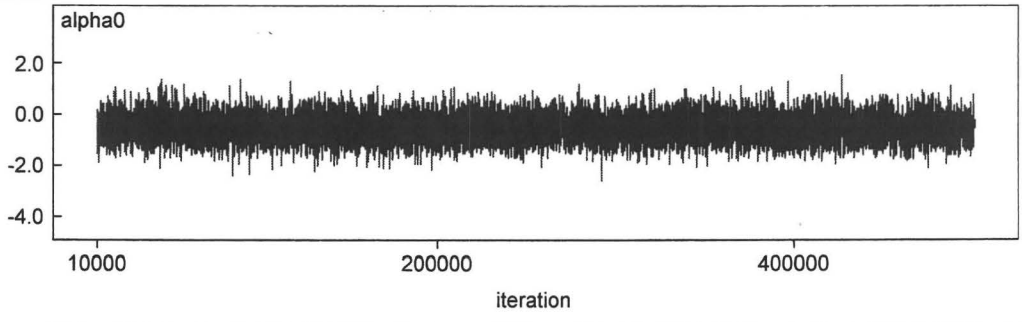
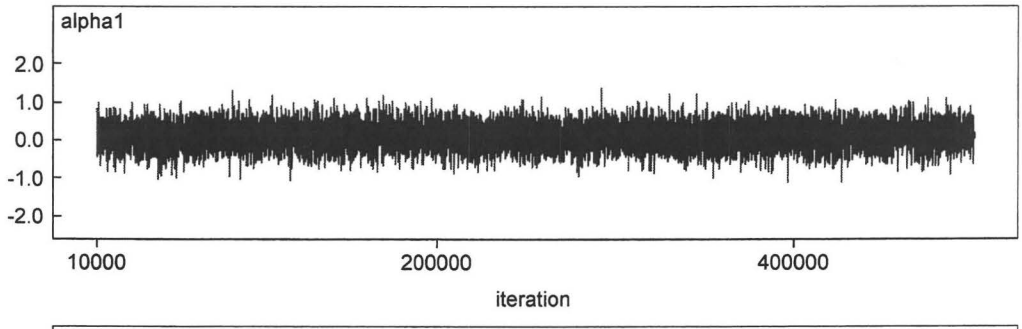
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5


tau sample: 490001
0.4
0.3
0.2
0.1
0.0
0.0
10.0
20.0

Time series


alpha0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
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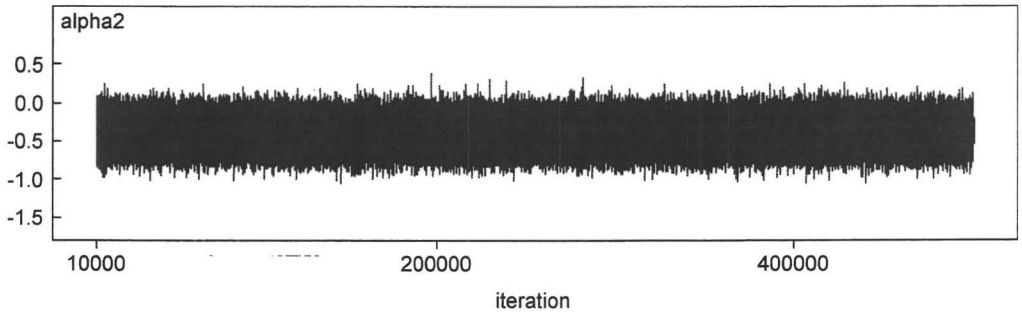
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


alpha2
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-0.5
-1.0
-1.5
10000
200000
400000
iteration

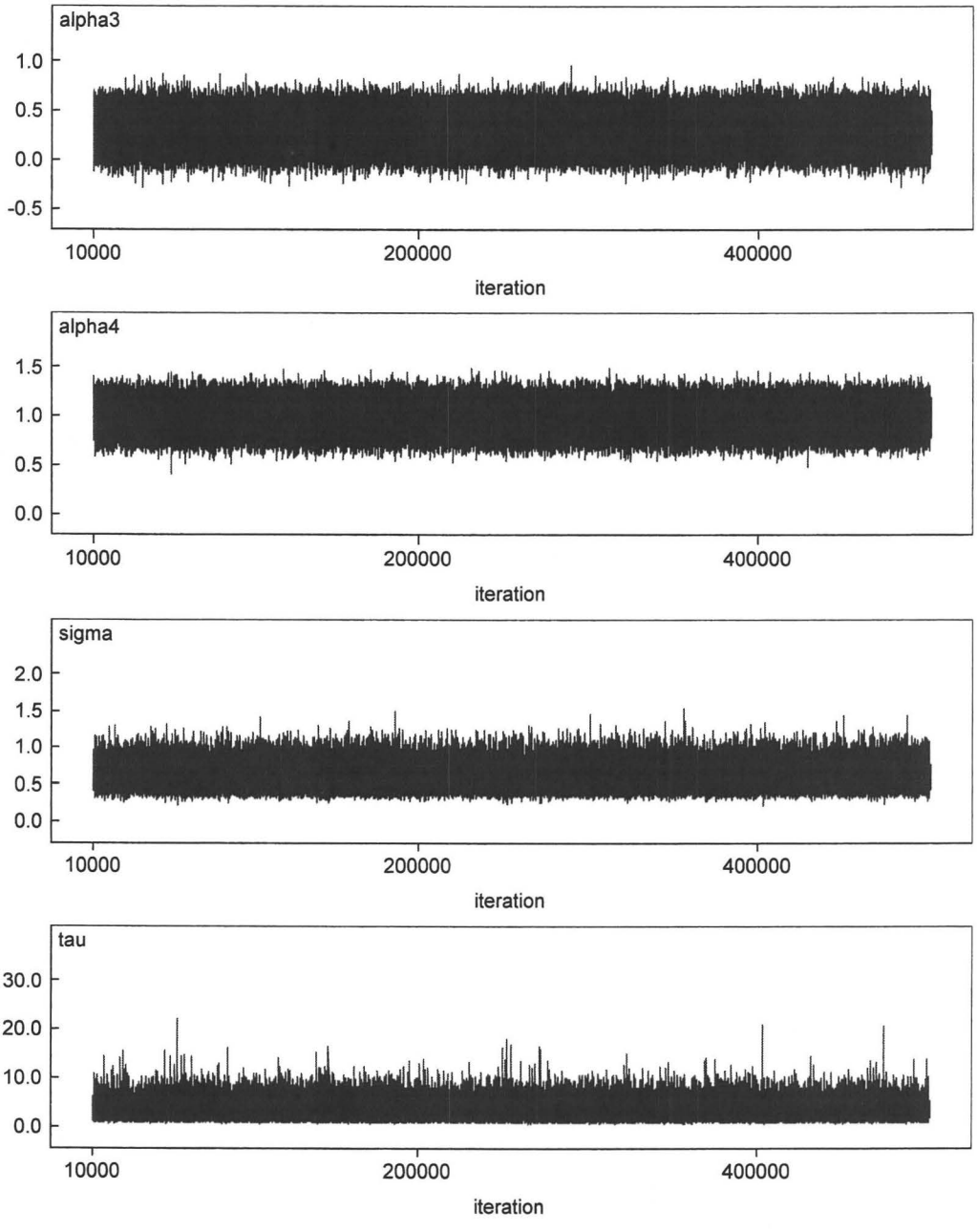
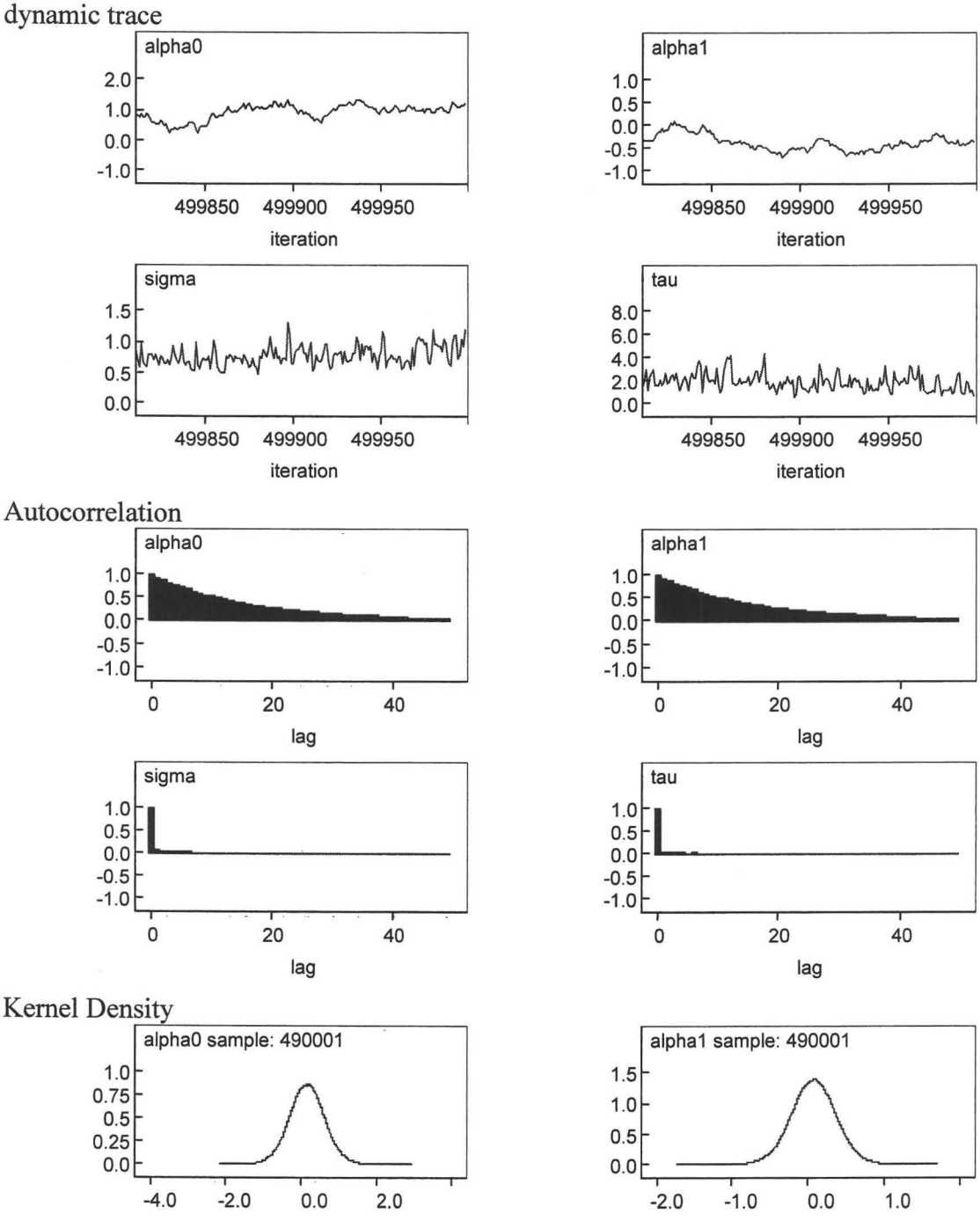
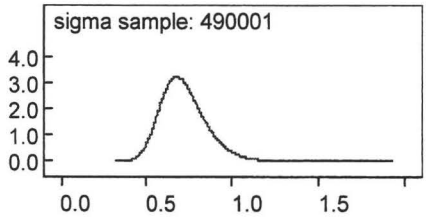

alpha3
1.0
0.5
0.0
-0.5
10000
200000
400000
iteration
alpha4
1.5
1.0
0.5
0.0
10000
200000
400000
iteration
sigma
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration
tau
30.0
20.0
10.0
0.0
10000
200000
400000
iteration

Figure 14. Diagnosis Plot for Bayesian Analysis — Systolic BP Controlled (without covariates)

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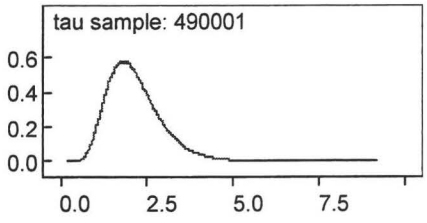
2.0
1.0
0.0
0.0
0.5
1.0
1.5


tau sample: 490001
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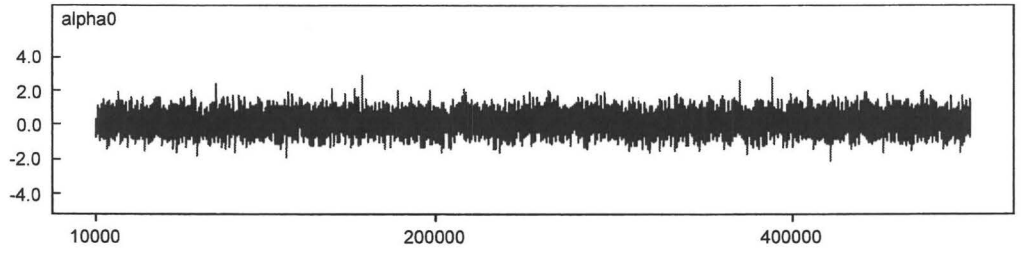
0.2
0.0
0.0
2.5
5.0
7.5

Time series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0.0
-2.0
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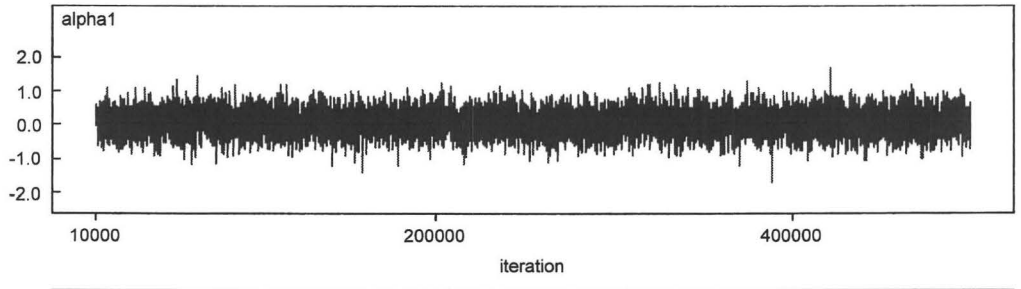
10000
200000
400000
iteration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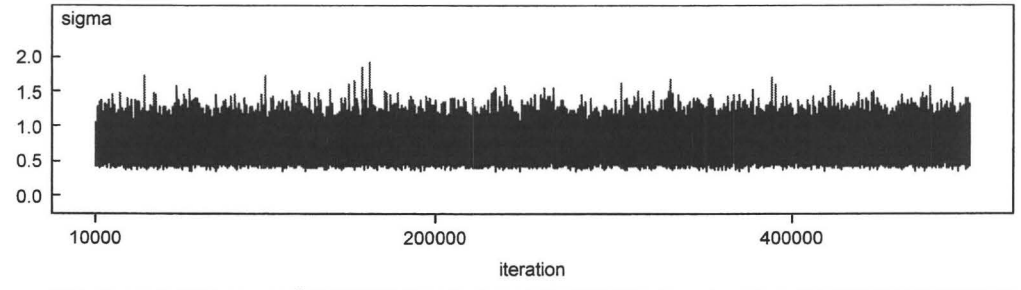
0.0
-1.0
-2.0
10000
200000
400000
iteration


sigma
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1.5
1.0
0.5
0.0
10000
200000
400000
iteration

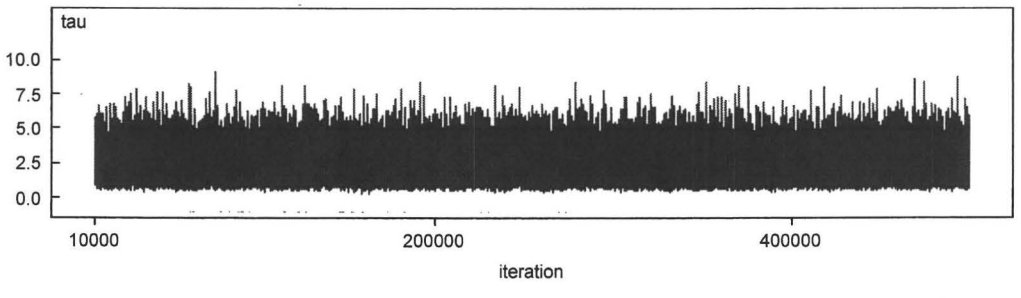
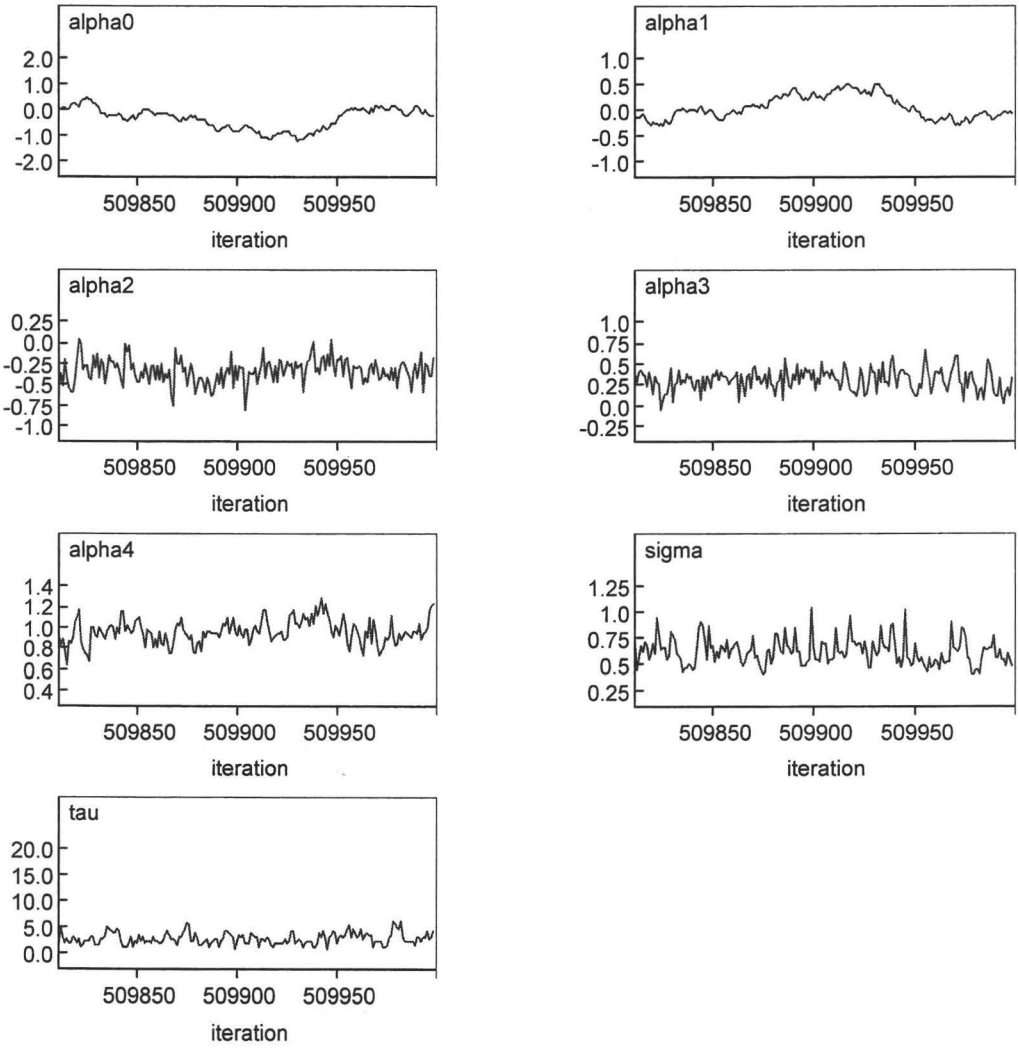
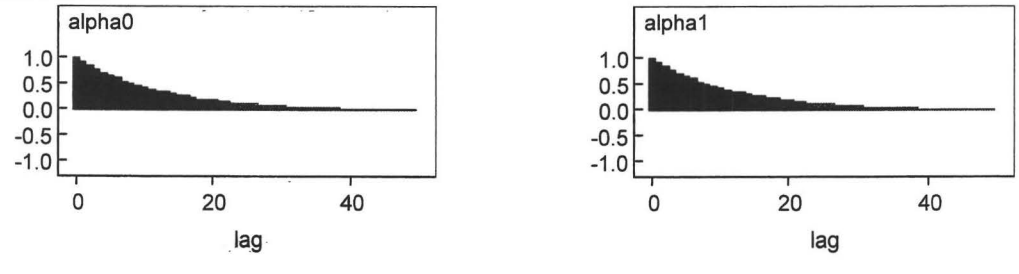

tau
10.0
7.5
5.0
2.5
0.0
10000
200000
400000
iteration

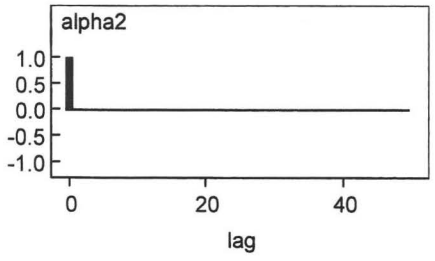
Figure 15. Diagnosis Plot for Bayesian Analysis — Systolic BP Controlled (with covariates)

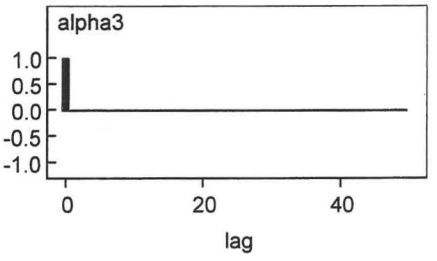
Dynamic trace

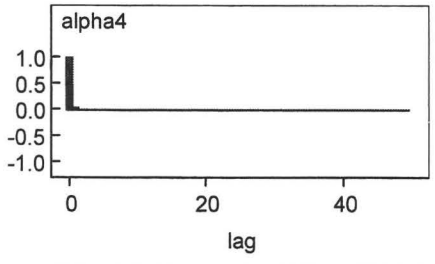


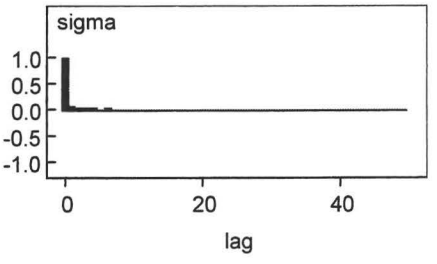
Autocorrelation

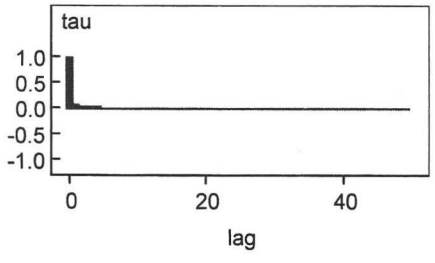




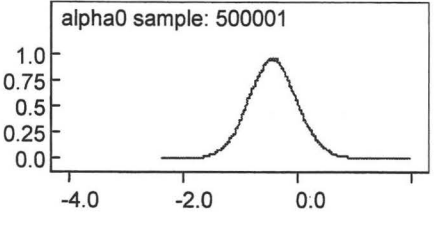


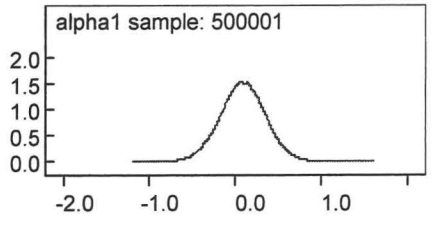


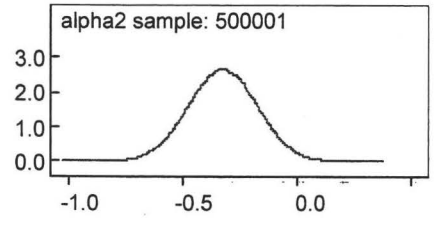


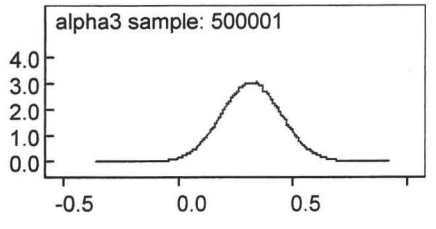


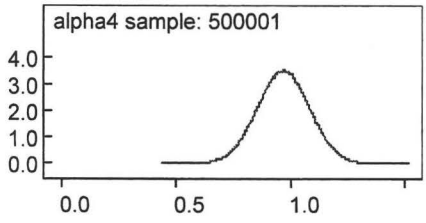
Kernel density

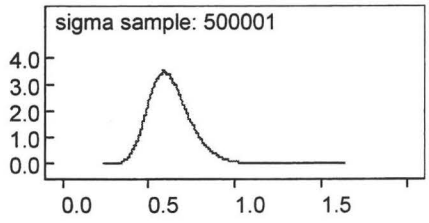


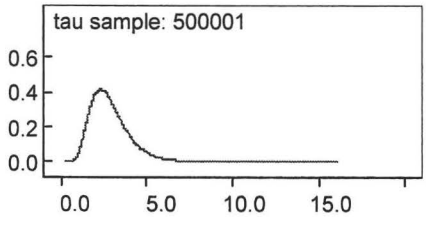




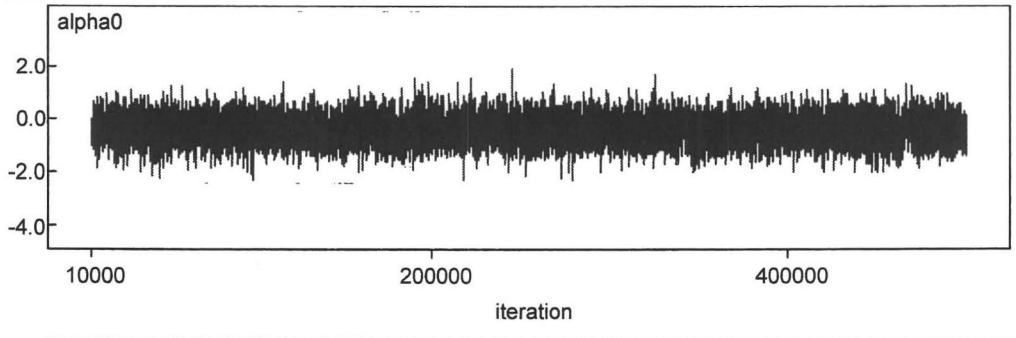


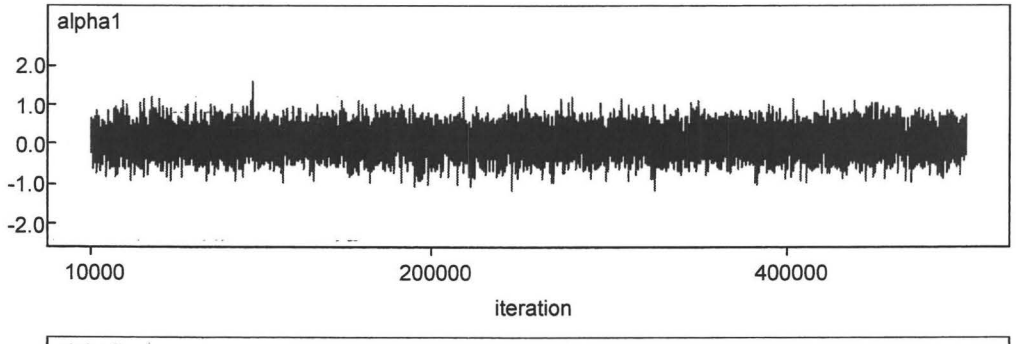

alpha4 sample: 500001
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0

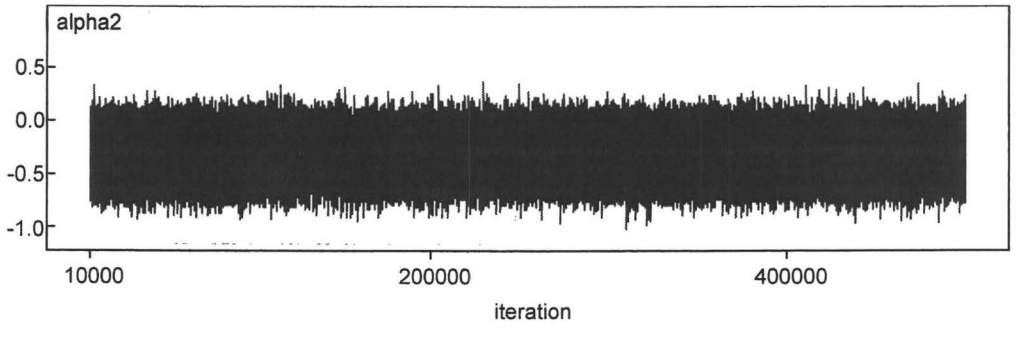

sigma sample: 500001
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5


tau sample: 500001
0.6
0.4
0.2
0.0
0.0
5.0
10.0
15.0

Time Series


alpha0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
2.0
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


alpha2
0.5
0.0
-0.5
-1.0
10000
200000
400000
iteration

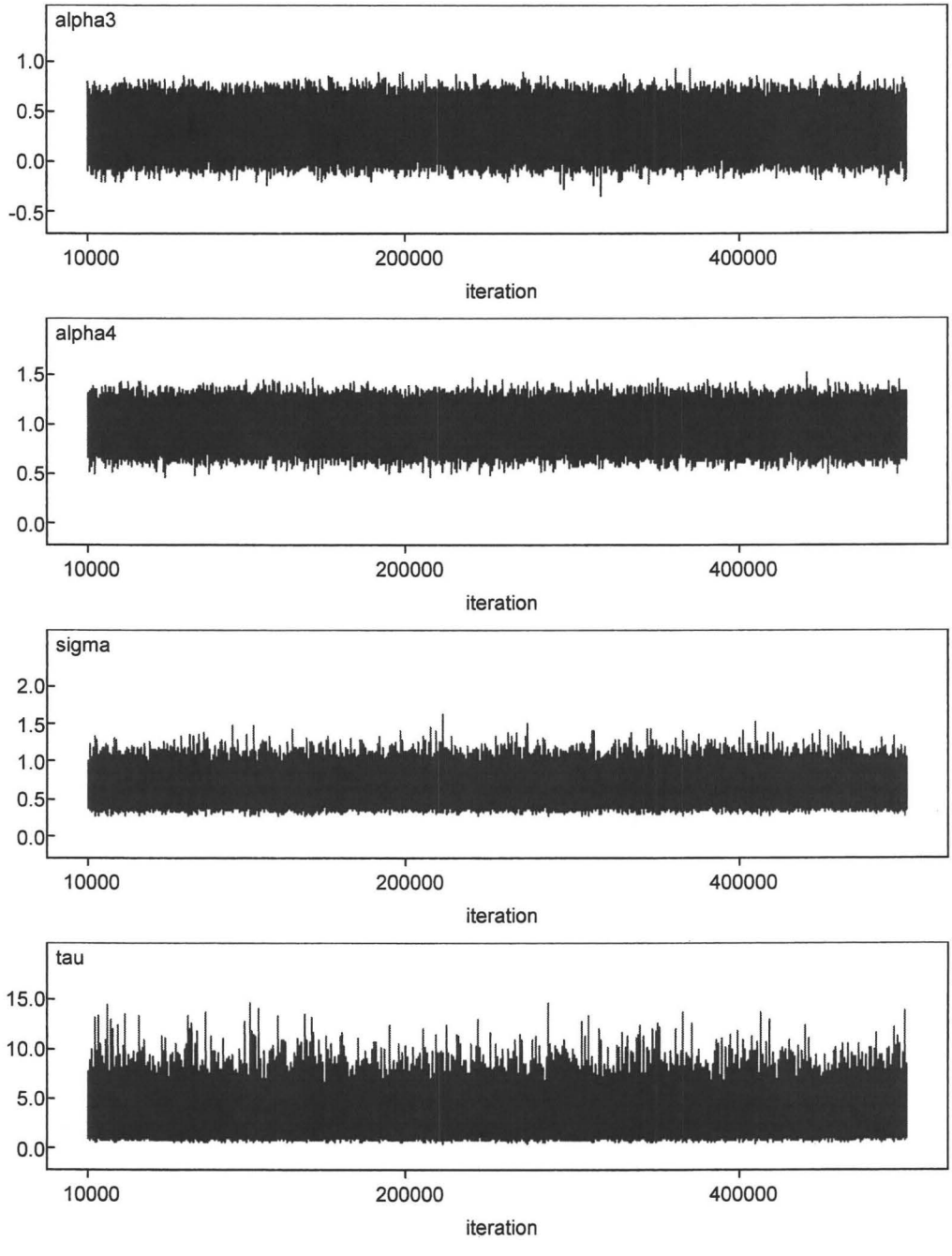
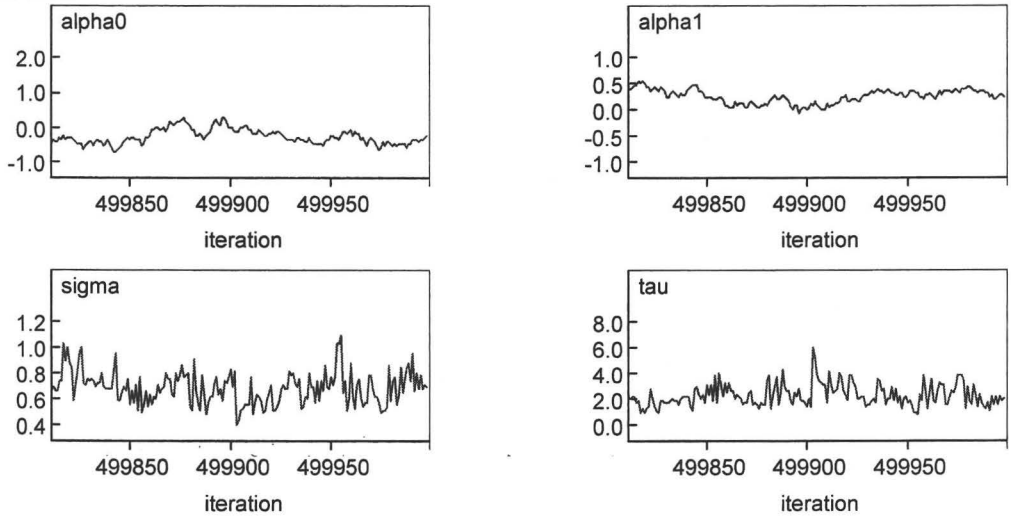
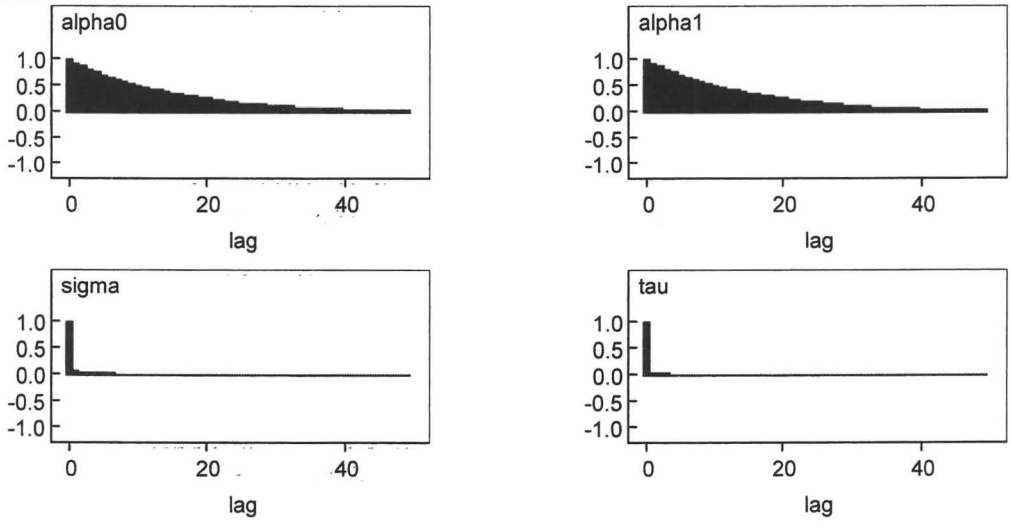

alpha3
1.0
0.5
0.0
-0.5
10000
200000
400000
iteration
alpha4
1.5
1.0
0.5
0.0
10000
200000
400000
iteration
sigma
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration
tau
15.0
10.0
5.0
0.0
10000
200000
400000
iteration

Figure 16. Diagnosis Plot for Bayesian Analysis — Average BP Controlled (without covariates)

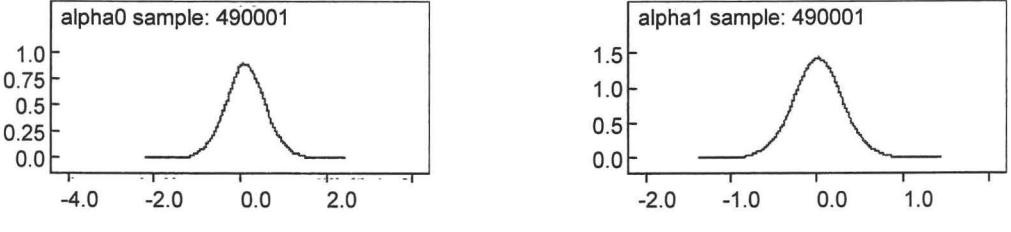
Dynamic trace

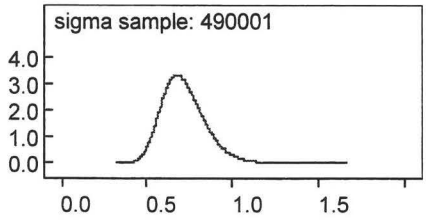


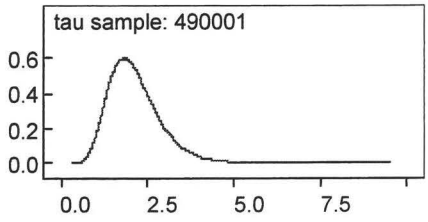
Autocorrelation



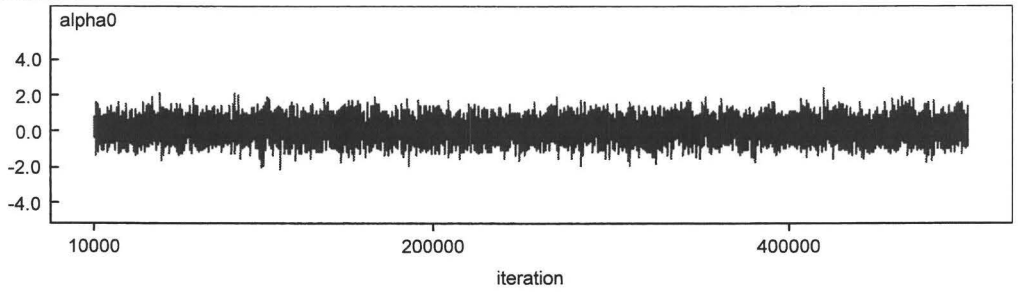
Kernel density

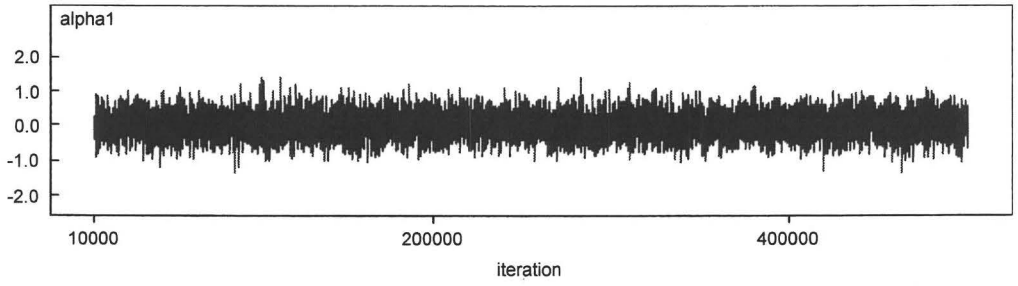


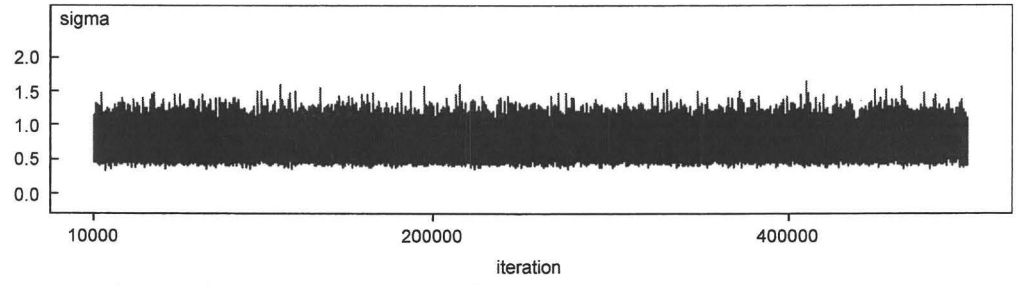

sigma sample: 490001
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5


tau sample: 490001
0.6
0.4
0.2
0.0
0.0
2.5
5.0
7.5

Time Series


alpha0
4.0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
2.0
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


sigma
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration

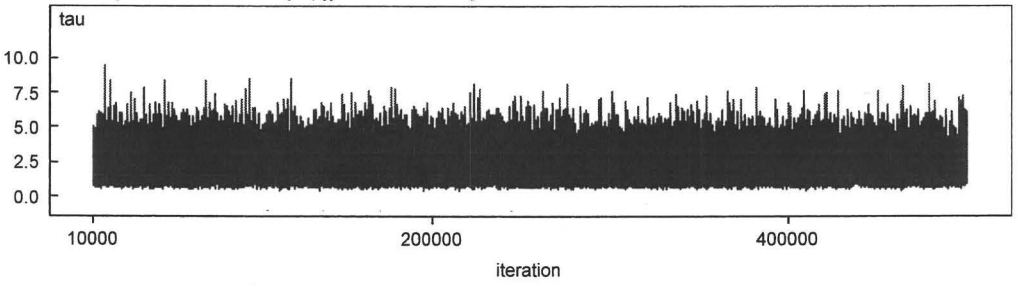
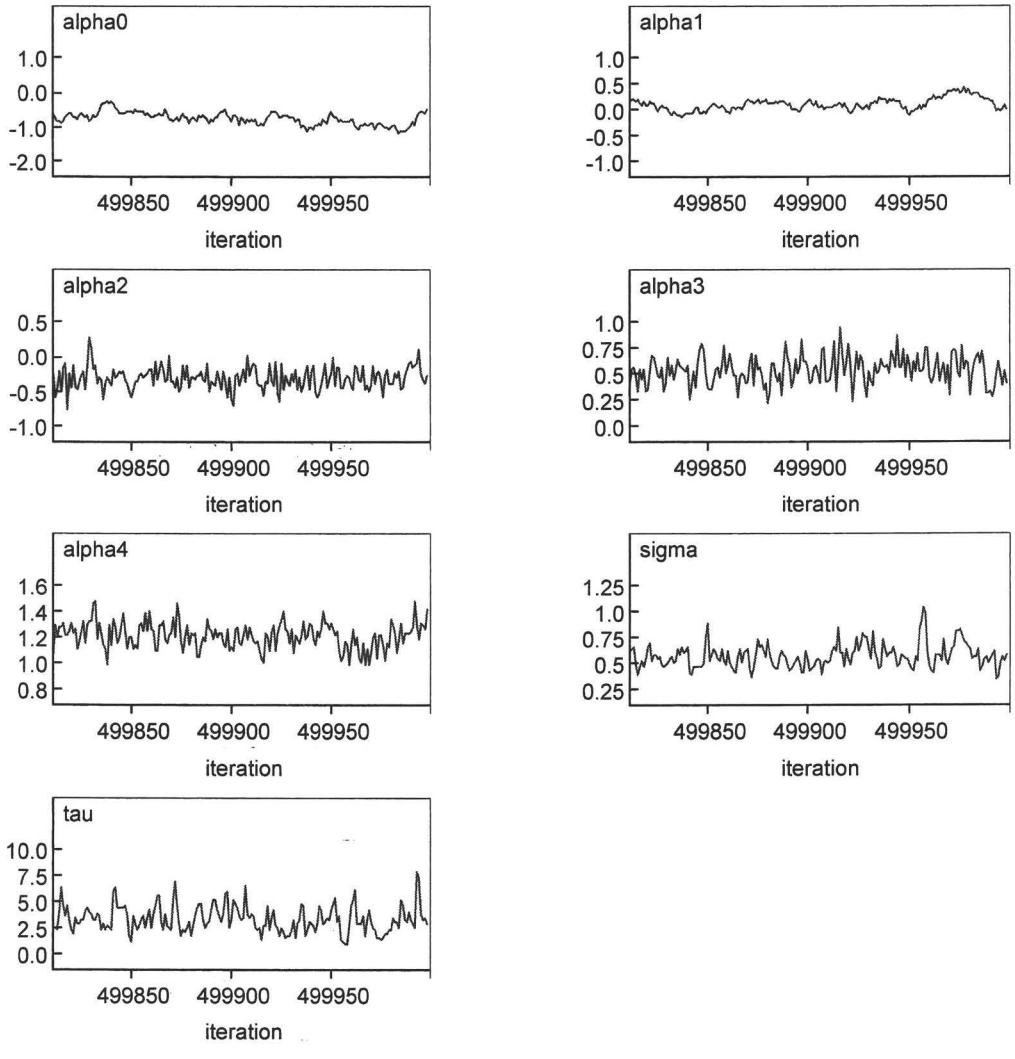
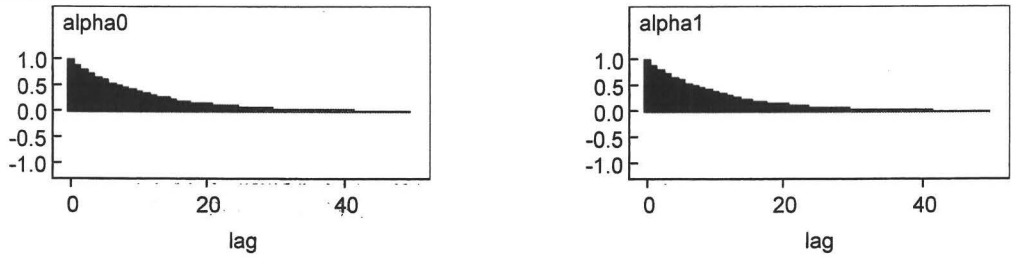

tau
10.0
7.5
5.0
2.5
0.0
10000
200000
400000
iteration

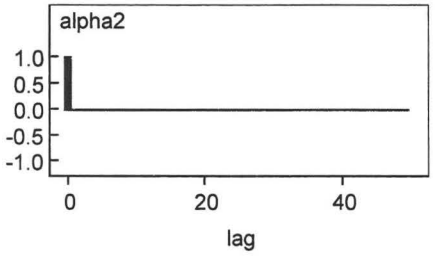
Figure 17. Diagnosis Plot for Bayesian Analysis — Average BP Controlled (with covariates)

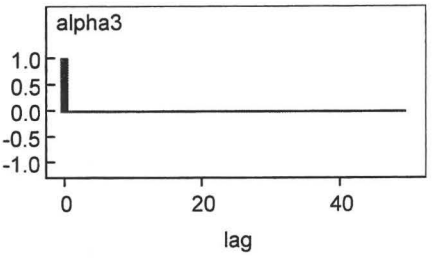
Dynamic trace

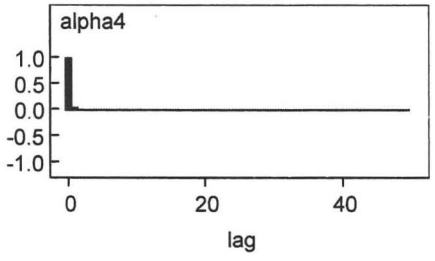


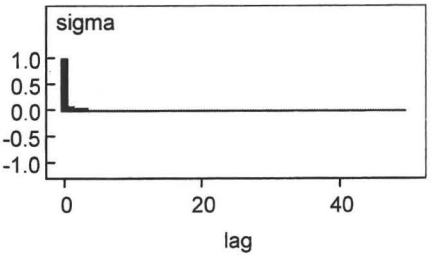
Autocorrelation

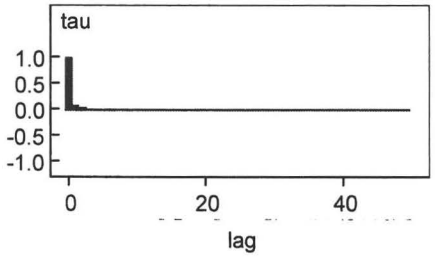




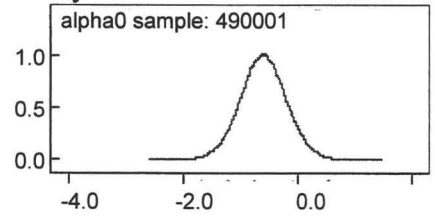


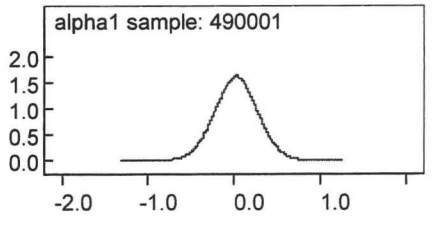


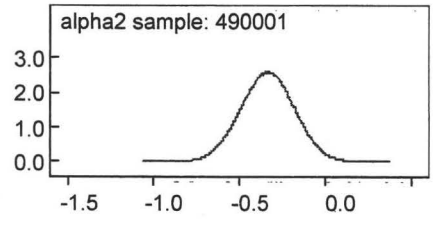


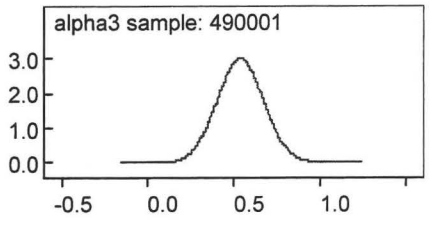


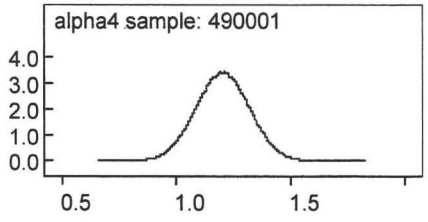
Kernel density

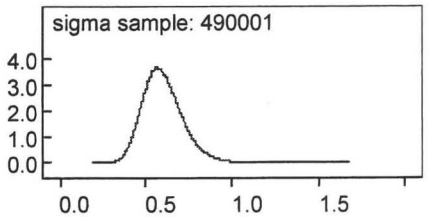


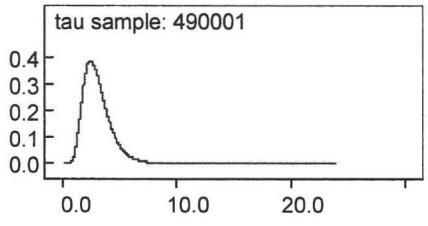




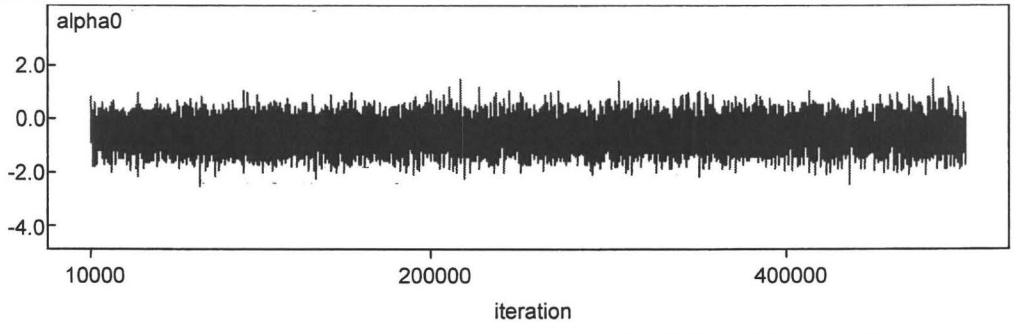


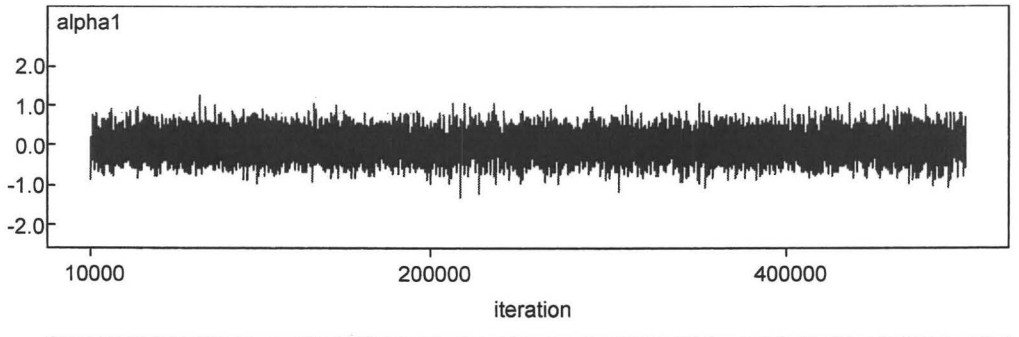

alpha4 sample: 490001
4.0
3.0
2.0
1.0
0.0
0.5
1.0
1.5

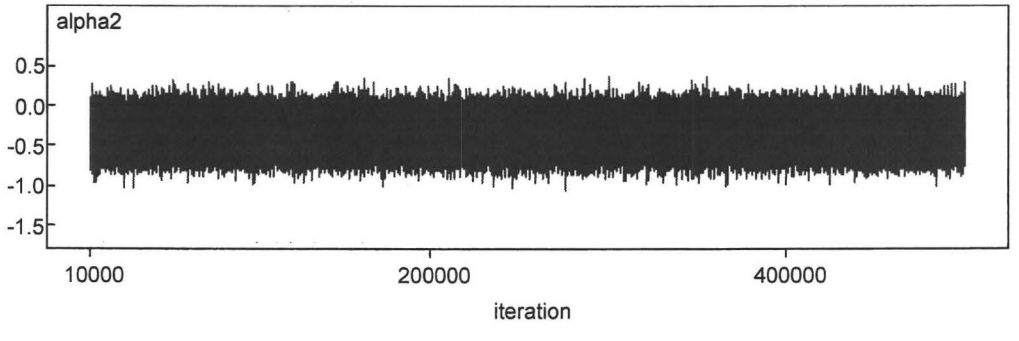

sigma sample: 490001
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5

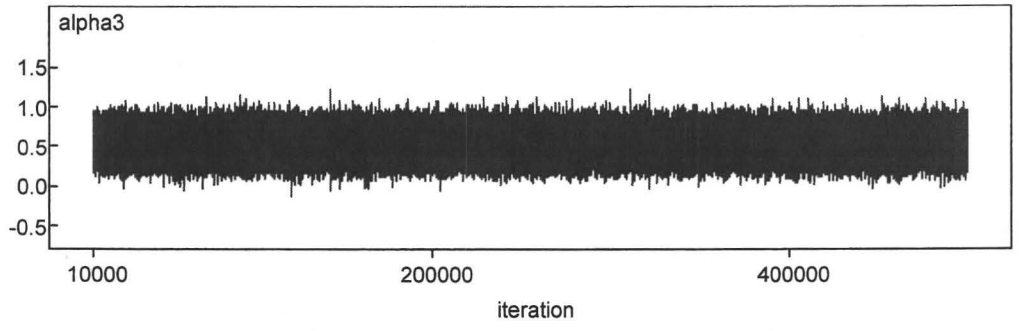

tau sample: 490001
0.4
0.3
0.2
0.1
0.0
0.0
10.0
20.0

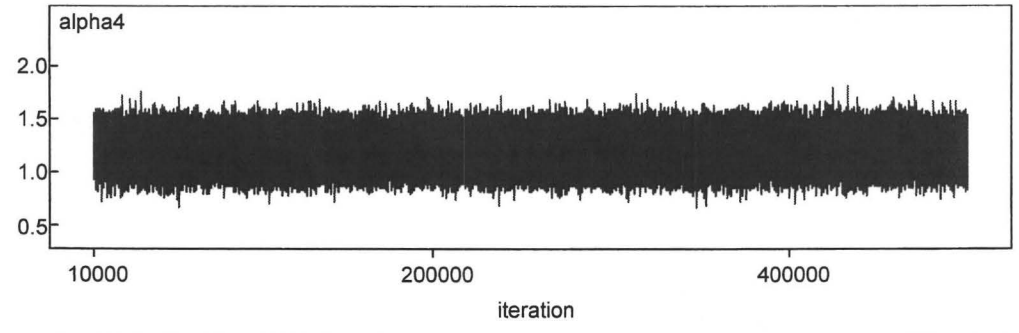
Time series

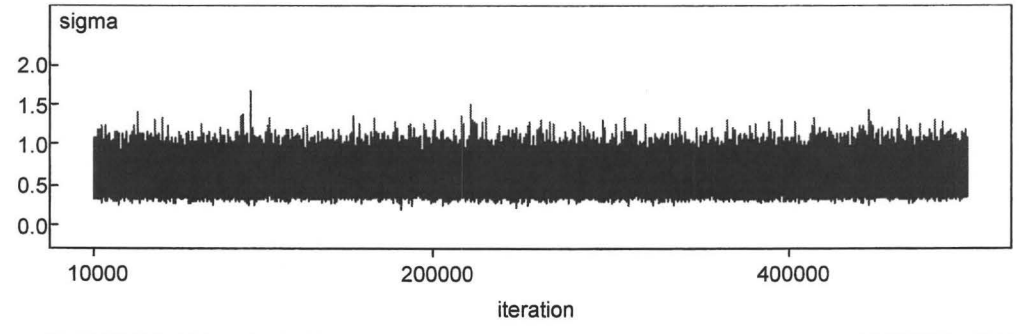

alpha0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
2.0
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


alpha2
0.5
0.0
-0.5
-1.0
-1.5
10000
200000
400000
iteration


alpha3
1.5
1.0
0.5
0.0
-0.5
10000
200000
400000
iteration


alpha4
2.0
1.5
1.0
0.5
10000
200000
400000
iteration


sigma
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration

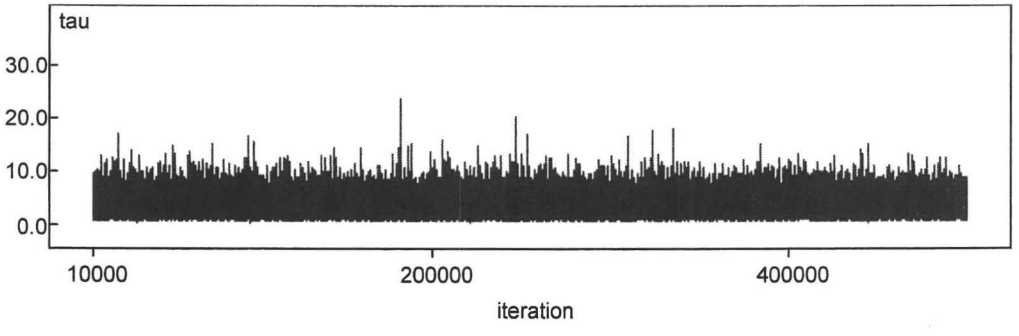
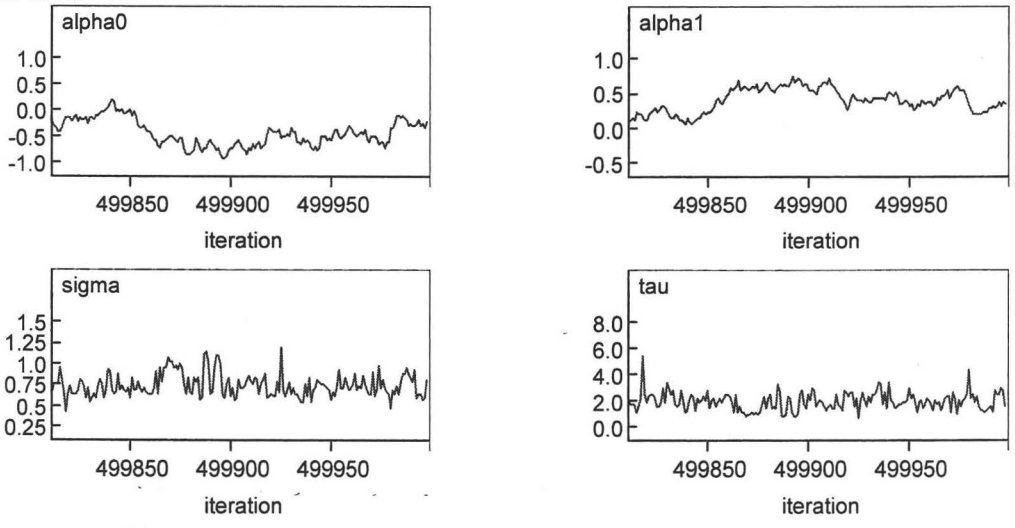
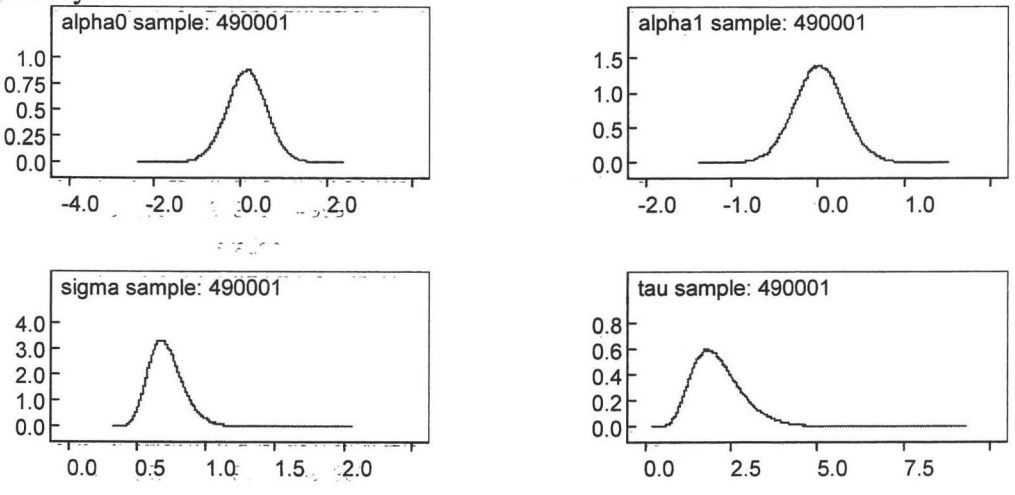

tau
30.0
20.0
10.0
0.0
10000
200000
400000
iteration

Figure 18. Diagnosis Plot for Bayesian Analysis — Average Systolic BP Controlled (without covariates)

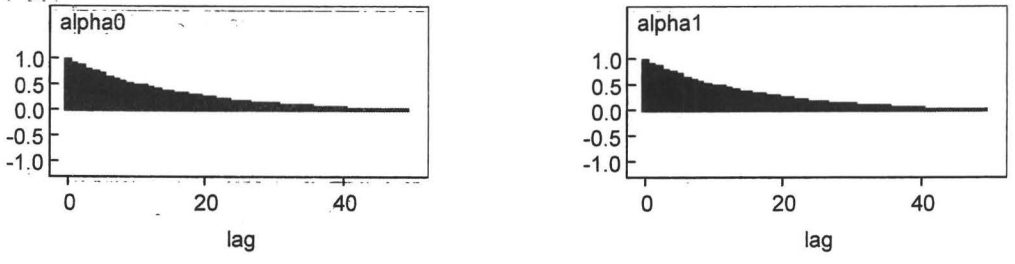
Dynamic trace

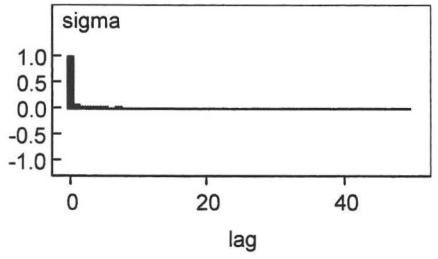


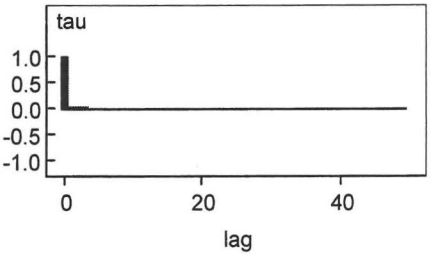
Kernel density



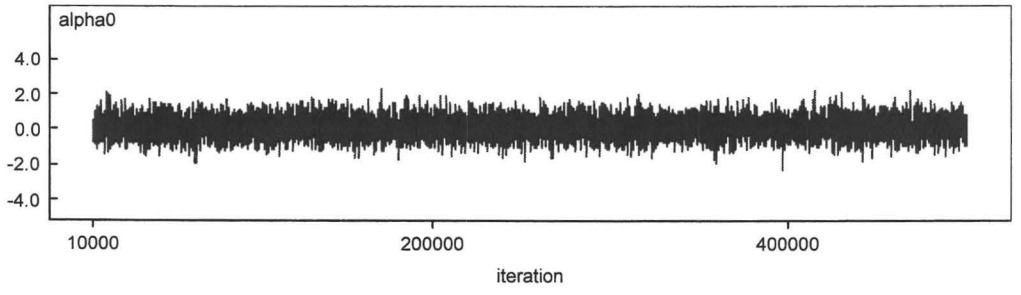
Autocorrelation

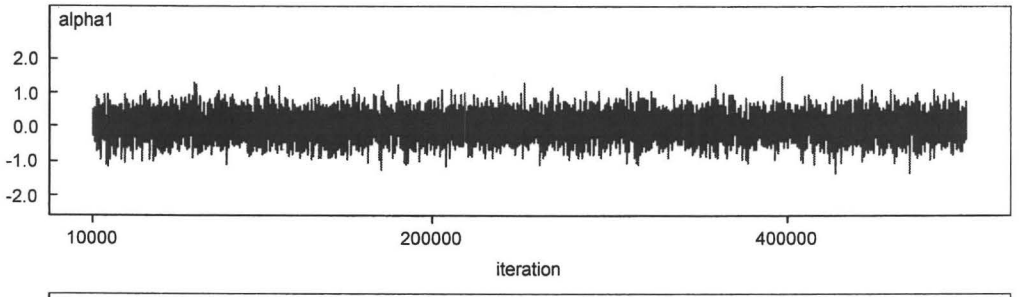


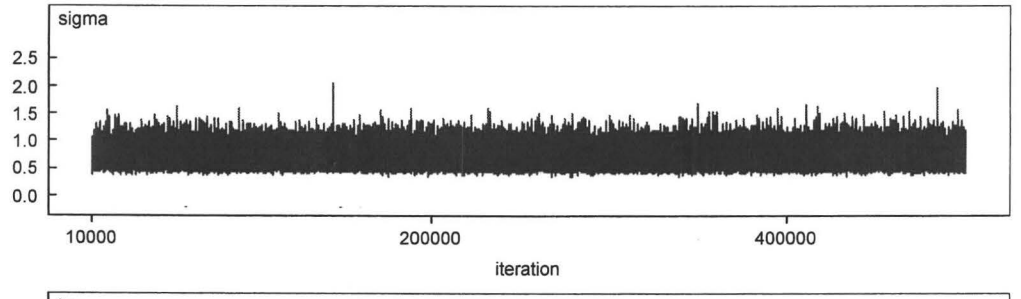

sigma
1.0
0.5
0.0
-0.5
-1.0
0
20
40
lag


tau
1.0
0.5
0.0
-0.5
-1.0
0
20
40
lag

Time series


alpha0
4.0
2.0
0.0
-2.0
-4.0
10000
200000
400000
iteration


alpha1
2.0
1.0
0.0
-1.0
-2.0
10000
200000
400000
iteration


sigma
2.5
2.0
1.5
1.0
0.5
0.0
10000
200000
400000
iteration

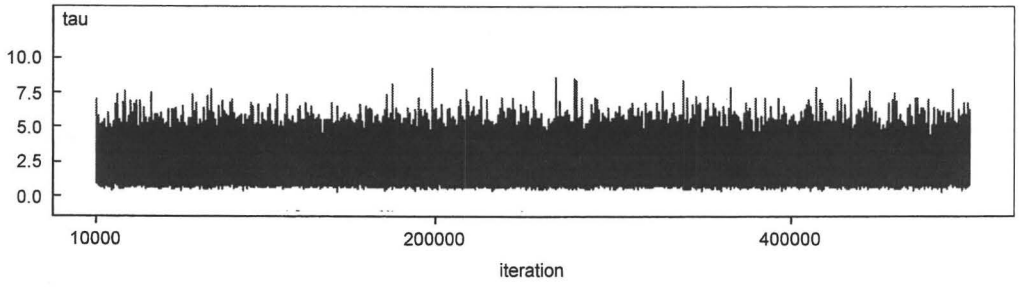
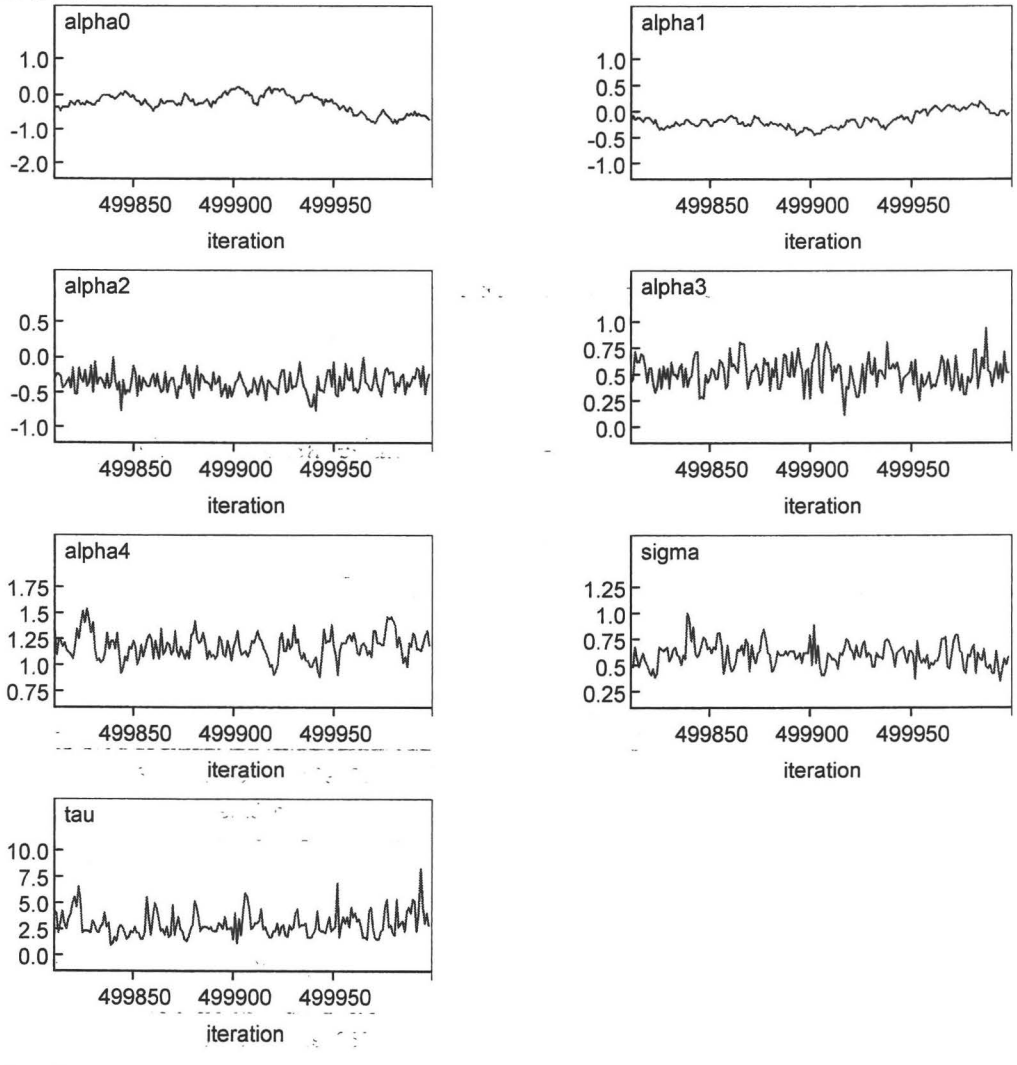
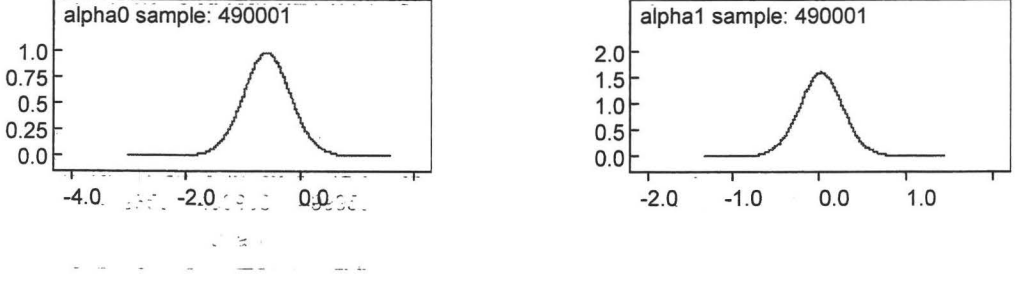

tau
10.0
7.5
5.0
2.5
0.0
10000
200000
400000
iteration

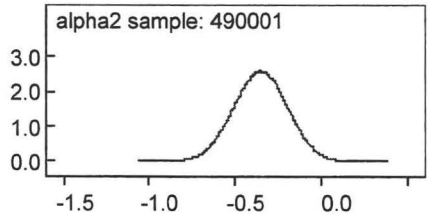
Figure 19. Diagnosis Plot for Bayesian Analysis — Average Systolic BP Controlled (with covariates)

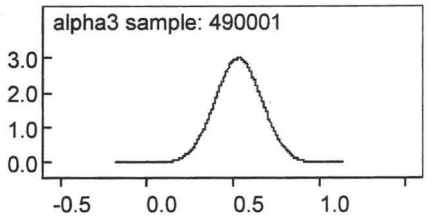
Dynamic trace

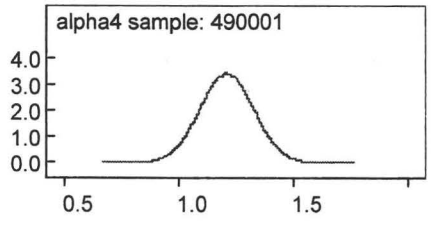


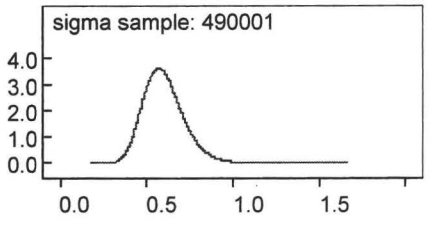
Kernel density

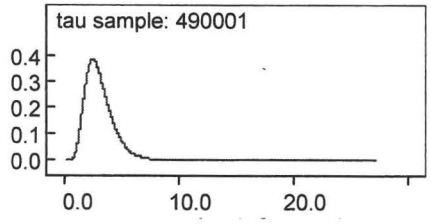












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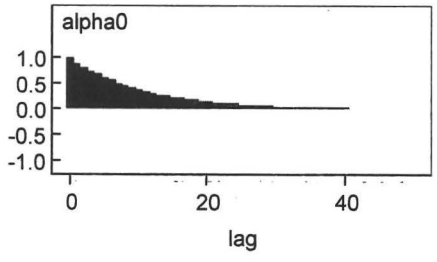

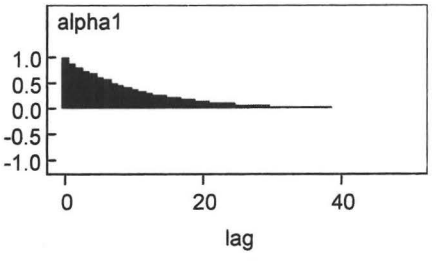

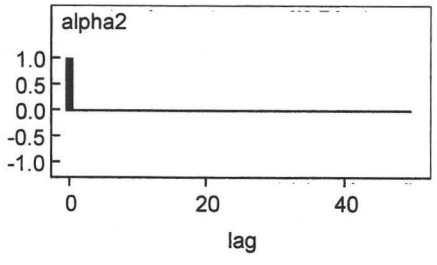

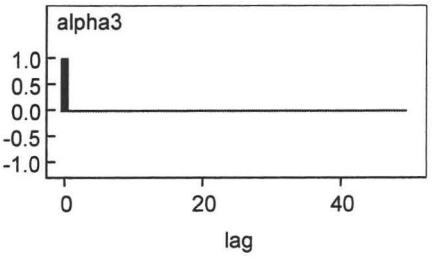

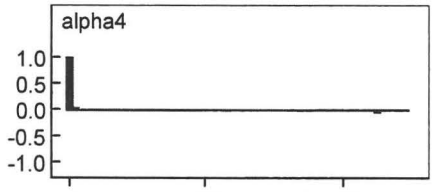
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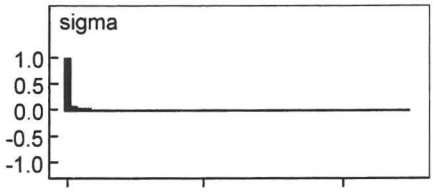
0.0
-0.5
-1.0
0
20
40
lag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0.0
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-1.0
0
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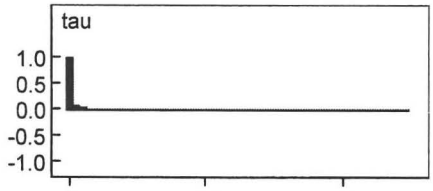
40
lag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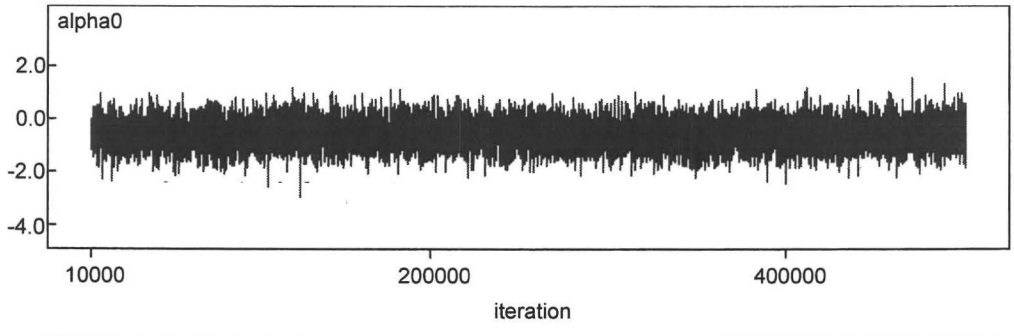
-0.5
-1.0
0
20
40
lag

Time series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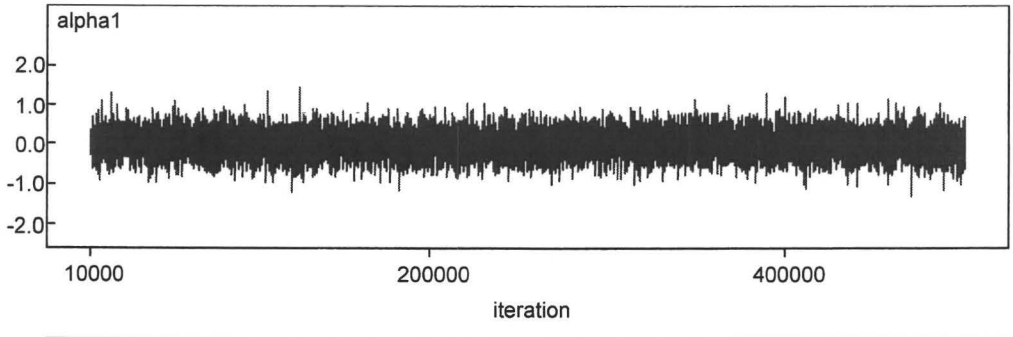
-4.0
10000
200000
400000
iteration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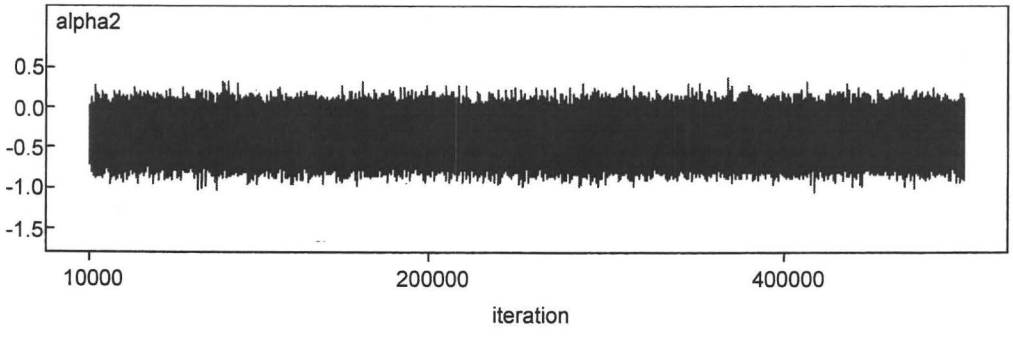
-2.0
10000
200000
400000
iteration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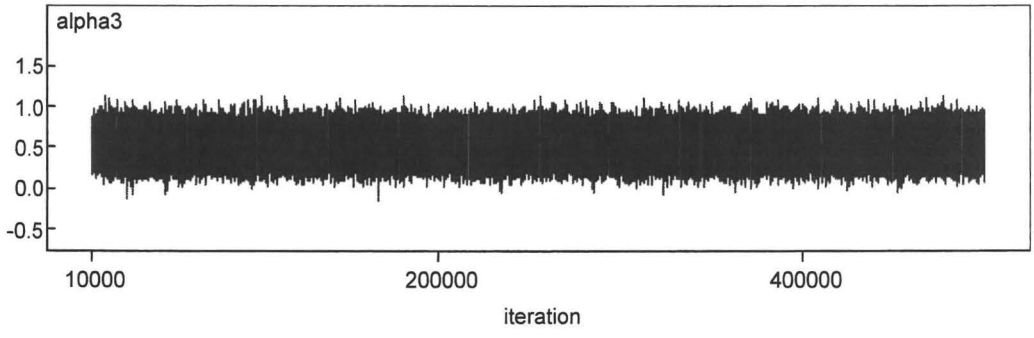
0.0
-0.5
-1.0
-1.5
10000
200000
400000
iteration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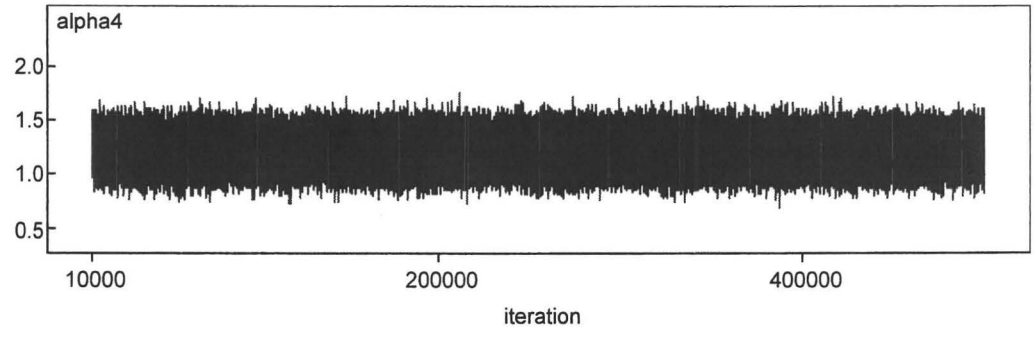
0.5
0.0
-0.5
10000
200000
400000
iteration


alpha4
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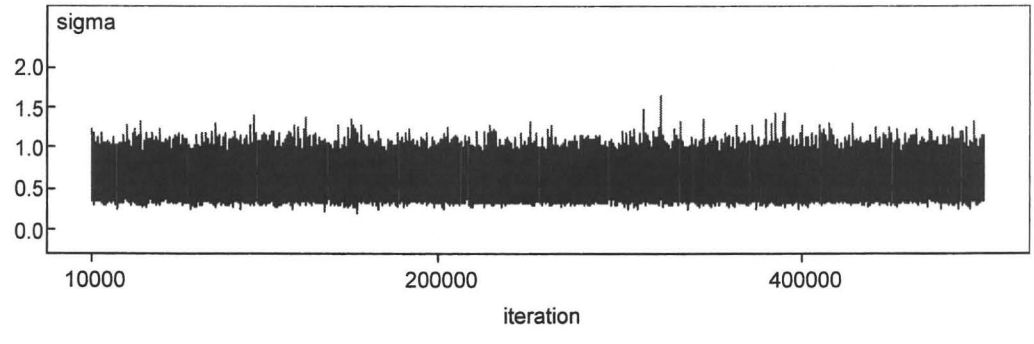
1.5
1.0
0.5
10000
200000
400000
iteration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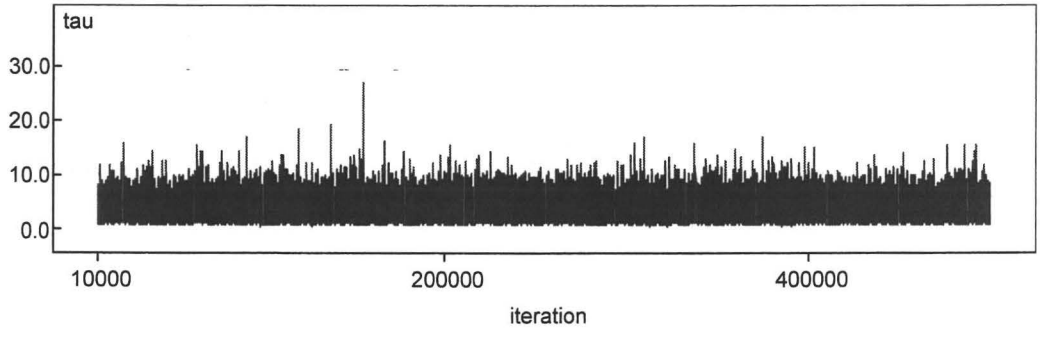
1.0
0.5
0.0
10000
200000
400000
iteration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10.0
0.0
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200000
400000
iteration

Appendix E

Tables

Table 1. Summary of Missing Values in The CHAT Trial

Patients' information at Baseline	**Num. of Missing in Control (n=770)**	**Num. of Missing in Intervention (n=770)**
Baseline Diagnostic Characteristics		
Diabetes	2	1
Heart Disease	1	3
Stroke or TIA	4	2
PVD	4	0
Smoke Status Changed	17	23
No Anti-hypertensive Medication Prescribed at Baseline	0	1
Hypertensive Status at Last Review	2	1
Retinopathy	4	1
Nephrophathy	4	3
Aortic Aneurysm	1	0
Demographic Information		
Gender	0	1
Age	0	1

Table 2. Patients Demographic Information

Demographic Information	**Control (n=770)**	**Intervention (n=769)**
Gender		
male(%)	319 (41%)	339 (44%)
Age (years) *		
mean(SD)	74.36 (6.22)	74.16 (6.14)

* **Age:** The number of years between the randomization date and the date of birth of the CHAT patient.

NOTE: The percentage is calculated based on the total number of patients in each study group.

Table 3. Baseline Diagnostic Characteristics of CHAT Patients

Health Conditions	**Control**	**Intervention**
Diabetes	n=768	n=769
disease(%)	123 (16%)	140 (18%)
Heart Disease	n=769	n=767
disease(%)	192 (25%)	201 (26%)
Stroke or TIA	n=766	n=768
disease(%)	41 (5%)	62 (8%)
PVD	n=766	n=770
disease(%)	22 (3%)	26 (3%)
Smoke Status Changed	n=753	n=747
no change(%)	586 (78%)	547 (73%)
No Anti-hypertensive Medication Prescribed at Baseline	n=770	n=769
medication(%)	415 (54%)	477 (62%)
Hypertensive Status at Last Review	n=768	n=769
disease(%)	384 (50%)	425 (55%)
Retinopathy	n=766	n=769
disease(%)	5 (1%)	5 (1%)
Nephrophathy	n=766	n=767
disease(%)	20 (3%)	31 (4%)
Aortic Aneurysm	n=769	n=770
disease(%)	14 (2%)	17 (2%)

NOTE: The percentage is calculated based on the total number of patients in each group of the CHAT trial.

Table 4. Comparison of Patients BP at Baseline and End of Trial

	Baseline		**End of Trial**	
	Control	**Intervention**	**Control**	**Intervention**
Systolic BP mean (SD)	136.14(17.92)	135.41(17.41)	135.74(17.84)	133.66(17.29)
Diastolic BP mean (SD)	74.88(9.11)	75.58(10.24)	73.88(9.90)	73.60(10.02)
Systolic BP controlled percentage	56%(428/770)	56%(428/770)	54%(417/770)	57%(439/770)
BP controlled percentage	55%(425/770)	55%(420/770)	53%(409/770)	56%(434/770)

Table 5. Results for Binary Outcome – BP Controlled

Unit of Analysis	Method of Analysis	No Adjustment for Covariates		Adjusting For Covariates *	
		OR	95% CI	OR	95% CI
Cluster	Un-weighted Regression	1.14	(0.71 1.83)	1.14	(0.72 1.81)
	Weighted Regression	1.30	(0.87 1.93)	1.30	(0.89 1.91)
	Random Effect Meta Regression (1)	1.09	(0.68 1.74)		
	Random Effect Meta Regression (2)	1.17	(0.72 1.90)		
Individual	Standard Logistic Regression	1.14	(0.93 1.39)	1.17	(0.95 1.44)
	Robust Standard Error	1.14	(0.72 1.80)	1.17	(0.79 1.73)
	Generalized Estimating Equations	1.14	(0.72 1.80)	1.15	(0.76 1.72)
	Random Effect Logistic Regression	1.10	(0.65 1.86)	1.13	(0.71 1.80)
	Bayesian Random Effect Regression	1.09	(0.61 1.94)	1.13	(0.68 1.87)

* For cluster-level analysis, include 'center' (i.e. Hamilton and Ottawa) as the covariate.

* For individual-level analysis, include 'diabetes at baseline', 'heart disease at baseline', and 'BP controlled at baseline' as the covariates. Other covariates (age, gender, experienced stroke or TIA, retinopathy, nephropathy, PVD and aortic aneurysm at baseline) were removed from the model since they were not significant.

(1) Fit the random effect meta regression model without adjusting the variance of log OR with VIF.
(2) Fit the random effect meta regression model with adjusting the variance of log OR with VIF.

Table 6. Results for Binary Outcome – Systolic BP Controlled

Unit of Analysis	Method of Analysis	No Adjustment for Covariates		Adjusting For Covariates *	
		OR	95% CI	OR	95% CI
Cluster	Un-weighted Regression	1.12	(0.70 1.81)	1.12	(0.71 1.78)
	Weighted Regression	1.30	(0.87 1.93)	1.30	(0.89 1.90)
	Random Effect Meta Regression (1)	1.07	(0.66 1.72)		
	Random Effect Meta Regression (2)	1.17	(0.72 1.89)		
Individual	Standard Logistic Regression	1.12	(0.92 1.37)	1.14	(0.92 1.40)
	Robust Standard Error	1.12	(0.71 1.78)	1.14	(0.76 1.70)
	Generalized Estimating Equations	1.12	(0.71 1.78)	1.11	(0.74 1.68)
	Random Effect Logistic Regression	1.07	(0.63 1.84)	1.10	(0.68 1.76)
	Bayesian Random Effect Regression	1.07	(0.60 1.93)	1.09	(0.64 1.84)

* For cluster-level analysis, include 'center' (i.e. Hamilton and Ottawa) as the covariate.

* For individual-level analysis, include 'diabetes at baseline', 'heart disease at baseline', and 'BP controlled at baseline' as the covariates. Other covariates (age, gender, experienced stroke or TIA, retinopathy, nephropathy, PVD and aortic aneurysm at baseline) were removed from the model since they were not significant.

(1) Fit the random effect meta regression model without adjusting the variance of log OR with VIF.
(2) Fit the random effect meta regression model with adjusting the variance of log OR with VIF.

Table 7. Results for Binary Outcome – Average BP Controlled

Unit of Analysis	Method of Analysis	No Adjustment for Covariates		Adjusting For Covariates *	
		OR	95% CI	OR	95% CI
Cluster	Un-weighted Regression	1.03	(0.63 1.69)	1.03	(0.65 1.64)
	Weighted Regression	1.12	(0.73 1.74)	1.12	(0.75 1.69)
	Random Effect Meta Regression (1)	1.00	(0.60 1.67)		
	Random Effect Meta Regression (2)	1.04	(0.64 1.69)		
Individual	Standard Logistic Regression	1.03	(0.84 1.26)	1.04	(0.84 1.29)
	Robust Standard Error	1.03	(0.64 1.66)	1.04	(0.69 1.56)
	Generalized Estimating Equations	1.03	(0.64 1.66)	1.02	(0.67 1.54)
	Random Effect Logistic Regression	1.01	(0.59 1.72)	1.02	(0.64 1.63)
	Bayesian Random Effect Regression	1.01	(0.57 1.80)	1.02	(0.62 1.68)

* For cluster-level analysis, include 'center' (i.e. Hamilton and Ottawa) as the covariate.

* For individual-level analysis, include 'diabetes at baseline', 'heart disease at baseline', and 'BP controlled at baseline' as the covariates. Other covariates (age, gender, experienced stroke or TIA, retinopathy, nephropathy, PVD and aortic aneurysm at baseline) were removed from the model since they were not significant.

(1) Fit the random effect meta regression model without adjusting the variance of log OR with VIF.
(2) Fit the random effect meta regression model with adjusting the variance of log OR with VIF.

Table 8. Results for Binary Outcome – Average Systolic BP Controlled

Unit of Analysis	Method of Analysis	No Adjustment for Covariates		Adjusting For Covariates *	
		OR	95% CI	OR	95% CI
Cluster	Un-weighted Regression	1.04	(0.63 1.69)	1.04	(0.66 1.64)
	Weighted Regression	1.13	(0.73 1.75)	1.13	(0.76 1.69)
	Random Effect Meta Regression (1)	1.00	(0.61 1.66)		
	Random Effect Meta Regression (2)	1.05	(0.65 1.71)		
Individual	Standard Logistic Regression	1.04	(0.85 1.27)	1.04	(0.84 1.29)
	Robust Standard Error	1.04	(0.65 1.66)	1.04	(0.69 1.56)
	Generalized Estimating Equations	1.04	(0.65 1.66)	1.02	(0.67 1.54)
	Random Effect Logistic Regression	1.01	(0.59 1.73)	1.02	(0.64 1.62)
	Bayesian Random Effect Regression	1.01	(0.57 1.80)	1.02	(0.61 1.70)

* For cluster-level analysis, include 'center' (i.e. Hamilton and Ottawa) as the covariate.

* For individual-level analysis, include 'diabetes at baseline', 'heart disease at baseline', and 'BP controlled at baseline' as the covariates. Other covariates (age, gender, experienced stroke or TIA, retinopathy, nephropathy, PVD and aortic aneurysm at baseline) were removed from the model since they were not significant.

(1) Fit the random effect meta regression model without adjusting the variance of log OR with VIF.
(2) Fit the random effect meta regression model with adjusting the variance of log OR with VIF.

Table 9. Results for Secondary Outcomes

Secondary Outcome	Type	Estimate &95%CI	P-Value
If BP Monitored	**Binary**	OR Scale	
Random Effect Meta Regression		1.16 (0.73 1.86)	0.54
GEE (no adjustment for covariates)		1.15 (0.72 1.84)	0.56
GEE (with adjustment for covariates) *		1.22 (0.76 1.96)	0.40
Frequency of BP monitoring	**Counts**		
Linear Regression (no adjustment for covariates)		0.26 (-0.52 1.04)	0.51
Linear Regression (with adjustment for covariates)+		0.04 (-0.39 0.47)	0.87
Average Systolic BP	**Continuous**		
Weighted Linear Regression		3.90 (0.41 7.39)	0.04
Two Sample T-Test		2.42 (-1.40 6.24)	0.23
Wilcoxon Rank Sum Test		227	0.28
Random Effect Meta Regression (1)		2.29 (-1.06 5.64)	0.20
Random Effect Meta Regression (2)		1.66 (-2.06 5.38)	0.87
Average Diastolic BP	**Continuous**		
Weighted Linear Regression		0.52 (-1.44 2.48)	0.60
Two Sample T-Test		0.35 (-1.65 2.35)	0.73
Wilcoxon Rank Sum Test		205	0.95
Random Effect Meta Regression (1)		0.31 (-1.75 2.37)	0.29
Random Effect Meta Regression (2)		0.08 (-2.06 2.22)	0.07
Percent of Patient with BP Controlled at End of Trial	**Continuous**		
Weighted Linear Regression		0.04 (-0.10 0.18)	0.59
Random Effect Meta Regression (1)		0.03 (-0.07 0.13)	0.58
Random Effect Meta Regression (2)		0.02 (-0.10 0.14)	0.76
Percent of Patient with Systolic BP Controlled at End of Trial	**Continuous**		
Weighted Linear Regression		0.05 (-0.11 0.21)	0.41
Random Effect Meta Regression (1)		0.03 (-0.07 0.13)	0.64
Random Effect Meta Regression (2)		0.01 (-0.11 0.13)	0.84

Table 9. Results for Secondary Outcomes (Continued)

Secondary Outcome	Type	Estimate & 95%CI	P-Value
Difference of Percent of Patient with BP Controlled Between Baseline and End of Trial	**Continuous**		
Weighted Linear Regression		0.01 (-0.03 0.05)	0.65
Random Effect Meta Regression (1)		0.04 (-0.02 0.10)	0.19
Random Effect Meta Regression (2)		0.02 (-0.02 0.06)	0.39
Difference of Percent of Patient with Systolic BP Controlled Between Baseline and End of Trial	**Continuous**		
Weighted Linear Regression		0.01 (-0.03 0.05)	0.58
Random Effect Meta Regression (1)		0.03 (-0.03 0.09)	0.33
Random Effect Meta Regression (2)		0.02 (-0.02 0.06)	0.49

* Patients' hypertensive status at last review, PVD at baseline, if taking hypertensive medicine and if patients' smoking status changed are included in the model as covariates. Other covariates (age, gender, diabetes, heart disease, experienced stroke or TIA, retinopathy, nephropathy and aortic aneurysm at baseline) were removed from the model since they were not significant.

+ Patients' hypertensive status at last review, heart disease at baseline, if taking hypertensive medicine, age, if patient has nephropathy at baseline are included in the model as covariates. Other covariates (diabetes at baseline, experienced stroke or TIA, retinopathy, PVD, gender, and aortic aneurysm at baseline) were removed from the model since they were not significant.

(1) Fit the random effect meta regression model without adjusting the variance with VIF.
(2) Fit the random effect meta regression model with adjusting the variance with VIF.

Table 10. Comparison of the Impact of Different Priors on Bayesian Model

Prior		Outcome: BP controlled (without adjustment for covariates)	
Type of Prior	Prior Dist.	Odds Ratio	95% C.I.
Non-informative	Uniform (0, 1)	1.11	(0.64 1.92)
	Uniform(0, 5)	1.09	(0.61 1.94)
	Uniform(0, 10)	1.09	(0.61 1.94)
	Uniform(0, 50)	1.09	(0.61 1.94)
	Uniform(0, 100)	1.09	(0.61 1.94)
Conjugate	IGamma(0.001, 0.001)	1.11	(0.63 1.94)
	IGamma(0.01, 0.01)	1.11	(0.63 1.95)
	IGamma(0,1, 0.1)	1.12	(0.64 1.95)

Appendix F

Code

F1. WinBugs Codes for Bayesian Analysis

```
#####################################################################
#
#       model for BP controlled without adjustment for covariates
#
#####################################################################

model
{

        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- last_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        y_bpimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        tau<-1/(sigma*sigma)
        sigma ~ dunif(0,10)
}

#####################################################################
#
#       model for BP controlled with adjustment for covariates
#
#####################################################################


model
{

        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- last_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        x_diabbase[i,j] <- diabbase[(i-1)*55+j]
                        x_hdbase[i,j] <- hdbase[(i-1)*55+j]
```

```
                x_base_bpcontrolled[i,j] <- base_bpcontrolled[(i-1)*55+j]


                y_bpimproved[i,j] ~ dbern(p[i,j])

                logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + alpha2 * x_diabbase[i,j]
            + alpha3 * x_hdbase[i,j] + alpha4 * x_base_bpcontrolled[i,j]
            + u[i]
        }
    }

    alpha0 ~ dnorm(0, 1.0E-6)
    alpha1 ~ dnorm(0, 1.0E-6)
    alpha2 ~ dnorm(0, 1.0E-6)
    alpha3 ~ dnorm(0, 1.0E-6)
    alpha4 ~ dnorm(0, 1.0E-6)
    tau<-1/(sigma*sigma)
    sigma ~ dunif(0,10)

}


#####################################################################
#
#       model for systolic BP controlled without adjustment for covariates
#
#####################################################################


model
{

    for (i in 1:28)
    {
        u[i] ~ dnorm(0,tau);

        for (j in 1:55)
        {
            y_sysimproved[i,j] <- last_sysimproved[(i-1)*55+j]
            x_assigned[i,j] <- assigned[(i-1)*55+j]
            y_sysimproved[i,j] ~ dbern(p[i,j])

            logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
        }
    }

    alpha0 ~ dnorm(0, 1.0E-6)
    alpha1 ~ dnorm(0, 1.0E-6)
    tau<-1/(sigma*sigma)
    sigma ~ dunif(0,10)
}


#####################################################################
#
#       model for systolic BP controlled with adjustment for covariates
#
#####################################################################


model
{
```

```
        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                                y_sysimproved[i,j] <- last_sysimproved[(i-1)*55+j]
                                x_assigned[i,j] <- assigned[(i-1)*55+j]
                                x_hdbase[i,j] <- hdbase[(i-1)*55+j]
                                x_base_syscontrolled[i,j] <- base_syscontrolled[(i-1)*55+j]
                                x_diabbase[i,j] <- diabbase[(i-1)*55+j]


                                y_sysimproved[i,j] ~ dbern(p[i,j])

                                logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + alpha2 * x_diabbase[i,j]
                        + alpha3 * x_hdbase[i,j] + alpha4 * x_base_syscontrolled[i,j]
                        + u[i]

                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        alpha2 ~ dnorm(0, 1.0E-6)
        alpha3 ~ dnorm(0, 1.0E-6)
        alpha4 ~ dnorm(0, 1.0E-6)

        tau<-1/(sigma*sigma)
        sigma ~ dunif(0,10)
}


#############################################################################
#
#       model for average BP controlled without adjustment for covariates
#
#############################################################################


model
{

        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- ave_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        y_bpimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        tau<-1/(sigma*sigma)
        sigma ~ dunif(0,10)
}
```

```
#####################################################################
#
#       model for average BP controlled with adjustment for covariates
#
#####################################################################


model
{
        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- ave_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        x_diabbase[i,j] <- diabbase[(i-1)*55+j]
                        x_hdbase[i,j] <- hdbase[(i-1)*55+j]
                        x_base_bpcontrolled[i,j] <- ave_base_bpcontrolled[(i-1)*55+j]


                        y_bpimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + alpha2 * x_diabbase[i,j]
                    + alpha3 * x_hdbase[i,j] + alpha4 * x_base_bpcontrolled[i,j]
                    + u[i]
                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        alpha2 ~ dnorm(0, 1.0E-6)
        alpha3 ~ dnorm(0, 1.0E-6)
        alpha4 ~ dnorm(0, 1.0E-6)

        tau<-1/(sigma*sigma)
        sigma ~ dunif(0,10)
}

#####################################################################
#
#       model for average systolic BP controlled without adjustment for covariates
#
#####################################################################


model
{
        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_sysimproved[i,j] <- ave_sysimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        y_sysimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
```

```
		}
	}

	alpha0 ~ dnorm(0, 1.0E-6)
	alpha1 ~ dnorm(0, 1.0E-6)
	tau<-1/(sigma*sigma)
	sigma ~ dunif(0,10)
}


#########################################################################
#
#	model for average systolic BP controlled with adjustment for covariates
#
#########################################################################


model
{

	for (i in 1:28)
	{
		u[i] ~ dnorm(0,tau);

		for (j in 1:55)
		{
			y_sysimproved[i,j] <- ave_sysimproved[(i-1)*55+j]
			x_assigned[i,j] <- assigned[(i-1)*55+j]
			x_diabbase[i,j] <- diabbase[(i-1)*55+j]
			x_hdbase[i,j] <- hdbase[(i-1)*55+j]
			x_base_syscontrolled[i,j] <- ave_base_syscontrolled[(i-1)*55+j]


			y_sysimproved[i,j] ~ dbern(p[i,j])

			logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + alpha2 * x_diabbase[i,j]
		+ alpha3 * x_hdbase[i,j] + alpha4 * x_base_syscontrolled[i,j]
		+ u[i]
		}
	}

	alpha0 ~ dnorm(0, 1.0E-6)
	alpha1 ~ dnorm(0, 1.0E-6)
	alpha2 ~ dnorm(0, 1.0E-6)
	alpha3 ~ dnorm(0, 1.0E-6)
	alpha4 ~ dnorm(0, 1.0E-6)
	tau<-1/(sigma*sigma)
	sigma ~ dunif(0,10)
}
```

F2. WinBugs Codes for Sensitivity Analysis

```
#########################################################################
#
#	Sensitivity analysis: model for BP controlled without adjustment for covariates
#
#########################################################################


model
{
```

```
        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- last_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        y_bpimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        tau ~ dgamma(0.001, 0.001)
        # tau ~ dgamma(0.01, 0.01)
        # tau ~ dgamma(0.1, 0.1)
        sigma <- 1 / sqrt(tau)
}

model
{
        for (i in 1:28)
        {
                u[i] ~ dnorm(0,tau);

                for (j in 1:55)
                {
                        y_bpimproved[i,j] <- last_bpimproved[(i-1)*55+j]
                        x_assigned[i,j] <- assigned[(i-1)*55+j]
                        y_bpimproved[i,j] ~ dbern(p[i,j])

                        logit(p[i,j]) <- alpha0 + alpha1 * x_assigned[i,j] + u[i]
                }
        }

        alpha0 ~ dnorm(0, 1.0E-6)
        alpha1 ~ dnorm(0, 1.0E-6)
        tau<-1/(sigma*sigma)
        sigma ~ dunif(0,10)
        # sigma ~ dunif(0,1)
        # sigma ~ dunif(0,5)
        # sigma ~ dunif(0,50)
        # sigma ~ dunif(0,100)
}

#####################################################################
#
#       initial values
#
#####################################################################

seed 314159

# initial values when using inverse gamma prior (without adjustment for covariates)
list(
alpha0 = 0, alpha1 = 0, tau = 1,
u = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,0,0,0,0,0,0,0,0))

# initial values when using uniform prior (without adjustment for covariates)
```

```
list(
alpha0 = 0, alpha1 = 0, sigma = 1,
u = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,0,0,0,0,0,0,0))

# initial values when using inverse gamma prior (with adjustment for covariates)
list(
alpha0 = 0, alpha1 = 0, alpha2=0, alpha3=0, alpha4=0, tau = 1,
u = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,0,0,0,0,0,0,0))

# initial values when using uniform prior (with adjustment for covariates)
list(
alpha0 = 0, alpha1 = 0, alpha2=0, alpha3=0, alpha4=0, sigma = 1,
u = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,0,0,0,0,0,0,0))
```

F3. SAS Codes for Merge and Extract Data From Original Data Files

```
#############################################################
#
#                    Prepare data set for analysis
#                    1.CHAT data
#
#############################################################

data chat1;
set chat.chat_data;

array bpdat{77} bpdt51 bpdt52 bpdt53 bpdt54 bpdt55 bpdt56 bpdt57 bpdt58 bpdt59 bpdt510
bpdt511 bpdt512 bpdt513 bpdt514 bpdt515 bpdt516 bpdt517 bpdt518 bpdt519 bpdt520
bpdt521 bpdt522 bpdt523 bpdt524 bpdt525 bpdt526 bpdt527 bpdt528 bpdt529 bpdt530
bpdt531 bpdt532 bpdt533 bpdt534 bpdt535 bpdt536 bpdt537 bpdt538 bpdt539 bpdt540
bpdt541 bpdt542 bpdt543 bpdt544 bpdt545 bpdt546 bpdt547 bpdt548 bpdt549 bpdt550
bpdt551 bpdt552 bpdt553 bpdt554 bpdt555 bpdt556 bpdt557 bpdt558 bpdt559 bpdt560
bpdt561 bpdt562 bpdt563 bpdt564 bpdt565 bpdt566 bpdt567 bpdt568 bpdt569 bpdt570
bpdt571 bpdt572 bpdt573 bpdt574 bpdt575 bpdt576 bpdt577;

array bpsys{77} bpsys51 bpsys52 bpsys53 bpsys54 bpsys55 bpsys56 bpsys57 bpsys58 bpsys59 bpsys510
bpsys511 bpsys512 bpsys513 bpsys514 bpsys515 bpsys516 bpsys517 bpsys518 bpsys519 bpsys520
bpsys521 bpsys522 bpsys523 bpsys524 bpsys525 bpsys526 bpsys527 bpsys528 bpsys529 bpsys530
bpsys531 bpsys532 bpsys533 bpsys534 bpsys535 bpsys536 bpsys537 bpsys538 bpsys539 bpsys540
bpsys541 bpsys542 bpsys543 bpsys544 bpsys545 bpsys546 bpsys547 bpsys548 bpsys549 bpsys550
bpsys551 bpsys552 bpsys553 bpsys554 bpsys555 bpsys556 bpsys557 bpsys558 bpsys559 bpsys560
bpsys561 bpsys562 bpsys563 bpsys564 bpsys565 bpsys566 bpsys567 bpsys568 bpsys569 bpsys570
bpsys571 bpsys572 bpsys573 bpsys574 bpsys575 bpsys576 bpsys577;

array bpdia{77} bpdia51 bpdia52 bpdia53 bpdia54 bpdia55 bpdia56 bpdia57 bpdia58 bpdia59 bpdia510
bpdia511 bpdia512 bpdia513 bpdia514 bpdia515 bpdia516 bpdia517 bpdia518 bpdia519 bpdia520
bpdia521 bpdia522 bpdia523 bpdia524 bpdia525 bpdia526 bpdia527 bpdia528 bpdia529 bpdia530
bpdia531 bpdia532 bpdia533 bpdia534 bpdia535 bpdia536 bpdia537 bpdia538 bpdia539 bpdia540
bpdia541 bpdia542 bpdia543 bpdia544 bpdia545 bpdia546 bpdia547 bpdia548 bpdia549 bpdia550
bpdia551 bpdia552 bpdia553 bpdia554 bpdia555 bpdia556 bpdia557 bpdia558 bpdia559 bpdia560
bpdia561 bpdia562 bpdia563 bpdia564 bpdia565 bpdia566 bpdia567 bpdia568 bpdia569 bpdia570
bpdia571 bpdia572 bpdia573 bpdia574 bpdia575 bpdia576 bpdia577;

array sysbef {3} sysbef1-sysbef3;
array diabef {3} diabef1-diabef3;
array sysaft {3} sysaft1-sysaft3;
array diaaft {3} diaaft1-diaaft3;

tmpb=0;
do i=77 to 1 by -1;
if(bpdat[i]^=.) and (bpdat[i]<endper1) and (tmpb<3) then do;
        tmpb=tmpb+1;
        sysbef[tmpb]=bpsys[i];
```

```
        diabef[tmpb]=bpdia[i];
 end;
end;

tmpa=0;
do i=77 to 1 by -1;
if(bpdat[i]^=.) and (endper1<bpdat[i]<endper2) and (tmpa<3) then do;
        tmpa=tmpa+1;
        sysaft[tmpa]=bpsys[i];
        diaaft[tmpa]=bpdia[i];
 end;
end;


monfreq=0;
do i=77 to 1 by -1;
if(bpdat[i]^=.) and (endper1<bpdat[i]<endper2) then monfreq=monfreq+1;
end;

monfreqbase=0;
do i=77 to 1 by -1;
if(bpdat[i]^=.) and (beginper<bpdat[i]<endper1) then monfreqbase=monfreqbase+1;
end;

if sysaft[1]^=888 and sysaft[1]^=999 then lastsysaft=sysaft[1];
if diaaft[1]^=888 and diaaft[1]^=999 then lastdiaaft=diaaft[1];

if sysbef[1]^=888 and sysbef[1]^=999 then lastsysbef=sysbef[1];
if diabef[1]^=888 and diabef[1]^=999 then lastdiabef=diabef[1];

if lastsysbef=. then base_syscontrolled=0;
else do;
if (diabbase=1) then do;
        if (lastsysbef<=130) then base_syscontrolled=1;
        else base_syscontrolled=0;
 end;
else do;
        if (lastsysbef<=140) then base_syscontrolled=1;
        else base_syscontrolled=0;
 end;
end;

if (lastsysbef=. or lastdiabef=.) then base_bpcontrolled=0;
else do;
if (diabbase=1) then do;
        if (lastsysbef<=130 and lastdiabef<=80) then base_bpcontrolled=1;
        else base_bpcontrolled=0;
end;
else do;
        if (lastsysbef<=140 and lastdiabef<=90) then base_bpcontrolled=1;
        else base_bpcontrolled=0;
end;
end;

if tmpa>=3 then do;
avesysa=int((sysaft{1}+sysaft{2}+sysaft{3})/3);
avediaa=int((diaaft{1}+diaaft{2}+diaaft{3})/3);
end;
else if tmpa=2 then do;
avesysa=int((sysaft{1}+sysaft{2})/2);
avediaa=int((diaaft{1}+diaaft{2})/2);
end;

else if tmpa=1 then do;
avesysa=sysaft{1};
```

```
avediaa=diaaft{1};
end;

if tmpa>=1 then bpmonitored=1;
else bpmonitored=0;

if tmpb>=3 then do;
avesysb=int((sysbef{1}+sysbef{2}+sysbef{3})/3);
avediab=int((diabef{1}+diabef{2}+diabef{3})/3);
end;
else if tmpb=2 then do;
avesysb=int((sysbef{1}+sysbef{2})/2);
avediab=int((diabef{1}+diabef{2})/2);
end;
else if tmpb=1 then do;
avesysb=sysbef{1};
avediab=diabef{1};
end;

if avesysa=. or avediaa=. then ave_bpimproved=0;
else do;
if (diabbase=1) then do;
        if (avesysa<=130 and avediaa<=80) then ave_bpimproved=1;
        else ave_bpimproved=0;
 end;
else do;
        if (avesysa<=140 and avediaa<=90) then ave_bpimproved=1;
        else ave_bpimproved=0;
 end;
end;

if avesysa=. then ave_sysimproved=0;
else do;
if (diabbase=1) then do;
        if (avesysa<=130) then ave_sysimproved=1;
        else ave_sysimproved=0;
end;
else do;
        if (avesysa<=140) then ave_sysimproved=1;
        else ave_sysimproved=0;
end;
end;

if lastsysaft=. or lastdiaaft=. then last_bpimproved=0;
else do;
if (diabbase=1) then do;
        if (lastsysaft<=130 and lastdiaaft<=80) then last_bpimproved=1;
        else last_bpimproved=0;
end;
else do;
        if (lastsysaft<=140 and lastdiaaft<=90) then last_bpimproved=1;
        else last_bpimproved=0;
end;
end;

if lastsysaft=. then last_sysimproved=0;
else do;
if (diabbase=1) then do;
        if (lastsysaft<=130) then last_sysimproved=1;
        else last_sysimproved=0;
end;
else do;
        if (lastsysaft<=140) then last_sysimproved=1;
        else last_sysimproved=0;
 end;
```

```
end;


keep assigned assfpid pairedto beginper2 ptid hypstat diabbase retinobase nephrobase hdbase strokebase
pvdbase aortanbase smokchg nomedbase deceased tmpb avesysb avediab tmpa avesysa avediaa lastsysbef
lastdiabef lastsysaft lastdiaaft ave_bpimproved ave_sysimproved last_bpimproved last_sysimproved
bpmonitored monfreq monfreqbase base_bpcontrolled base_syscontrolled;
run;

proc print data=chat1;
run;

############################################################
#
#                    Prepare data set for analysis
#                    2.CHAT patient demographic data
#
############################################################

data chat2;
set chat.chat_all;
run;

proc print data=chat2;
run;


############################################################
#
#                    Prepare data set for analysis
#                    3. merge CHAT data with the CHAT patient demographic data
#
############################################################

proc sort data=chat1;
by ptid;
run;

proc sort data=chat2;
by ptid;
run;

options yearcutoff=1907;
data chat.chatmerge;
merge chat1 chat2;
by ptid;
age=intck('year',input(dob,mmddyy8.),beginper2);
drop fpid;
run;

proc print data=chat.chatmerge;
run;
```

F4. SAS Codes for Descriptive Statistics of Demographic Information

```
############################################################
#
#                    Patients characteristic statistics
#
############################################################


proc sql;
select trim(assfpid), int(mean(age)*100)/100 as mean_age,int(sqrt(var(age))*100)/100 as se_age
```

```
from chat.chatmerge
group by assfpid;


proc sql;
select ptid
from chat.chatmerge
where age=.;


proc sql;
select trim(assfpid), sum(sex=1) as male, sum(sex=1)/55 as per_male, sum(sex=2) as female, sum(sex=2)/55 as
        per_female
from chat.chatmerge
group by assfpid, sex;


proc sql;
select assigned, sum(sex=1) as male, sum(sex=2) as female
from chat.chatmerge
group by assigned, sex;
```

F5. SAS Codes for Descriptive Statistics of Baseline Diagnostic Characteristics

```
#############################################################
#
#          Patients characteristic statistics
#
#############################################################


proc sql;
select assigned, sum(diabbase=1) as disease, sum(diabbase=0) as nodisease,
      sum(diabbase<>0 and diabbase<>1) as missing
from chat.chatmerge
group by assigned;



proc sql;
select assigned, sum(hdbase=1) as disease, sum(hdbase=0) as nodisease,
       sum(hdbase<>0 and hdbase<>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(strokebase =1) as disease, sum(strokebase =0) as nodisease,
       sum(strokebase <>0 and strokebase <>1) as missing
from chat.chatmerge
group by assigned;
proc sql;
select assigned, sum(pvdbase =1) as disease, sum(pvdbase =0) as nodisease,
       sum(pvdbase <>0 and pvdbase <>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(retinobase =1) as disease, sum(retinobase =0) as nodisease,
       sum(retinobase <>0 and retinobase <>1) as missing
from chat.chatmerge
group by assigned;
```

```
proc sql;
select assigned, sum(nephrobase =1) as disease, sum(nephrobase =0) as nodisease,
        sum(nephrobase <>0 and nephrobase <>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(aortanbase =1) as disease, sum(aortanbase =0) as nodisease,
        sum(aortanbase <>0 and aortanbase <>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(hypstat =1) as disease, sum(hypstat =0) as nodisease,
        sum(hypstat <>0 and hypstat <>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(nomedbase =1) as disease, sum(nomedbase =0) as nodisease,
        sum(nomedbase <>0 and nomedbase <>1) as missing
from chat.chatmerge
group by assigned;


proc sql;
select assigned, sum(smokchg =0) as change0, sum(smokchg =1) as change1,  sum(smokchg =2) as change2,
        sum(smokchg<>1 and smokchg<>2 and smokchg<>0) as missing
from chat.chatmerge
group by assigned;
```

F6. SAS Codes for Cluster-Level Analysis of Primary Outcomes

```
############################################################
#
#         Prepare code for cluster-level analysis
#
############################################################


data chat.cluster_chat;
set chat.chatmerge;
keep assigned assfpid pairedto ave_bpimproved ave_sysimproved last_bpimproved last_sysimproved bpmonitored;
run;


proc SQL;
select   trim(assfpid)   as   Assfpid,   trim(pairedto)   as   Pairedto,   sum(input(assigned,2.0))/55   as   Assign,
          sum(ave_bpimproved) as Ave_bp,
sum(ave_sysimproved) as Ave_sys, sum(last_bpimproved) as Last_bp, sum(last_sysimproved) as Last_sys,
sum(bpmonitored) as Bpmonitored
from chat.cluster_chat
group by assfpid, pairedto;


data cluster;
input assfpid $ pairedto $ center $ assigned $ ave_bpimproved ave_sysimproved last_bpimproved last_sysimproved
          bpmonitored N;
```

```
datalines;
     H-01   H-02   H      1    11    11    15    16    41    55
     H-02   H-01   H      2    32    32    36    36    50    55
     H-03   H-04   H      2    22    22    24    24    45    55
     H-04   H-03   H      1    20    20    19    19    40    55
     H-05   H-06   H      1    26    26    24    24    44    55
     H-06   H-05   H      2    22    23    24    25    39    55
     H-07   H-08   H      2    25    25    33    33    41    55
     H-08   H-07   H      1    46    46    48    48    51    55
     H-09   H-10   H      2    20    20    24    24    41    55
     H-10   H-09   H      1    28    28    29    30    39    55
     H-11   H-12   H      1    21    21    20    20    49    55
     H-12   H-11   H      2    25    25    27    27    43    55
     H-13   H-14   H      1    22    22    27    28    44    55
     H-14   H-13   H      2    34    34    34    34    49    55
     O-01   O-03   O      1    39    40    39    40    51    55
     O-02   O-04   O      1    18    18    20    20    40    55
     O-03   O-01   O      2    23    24    25    25    39    55
     O-04   O-02   O      2    33    33    36    36    46    55
     O-05   O-08   O      1    41    41    39    39    52    55
     O-06   O-07   O      2    35    35    36    37    45    55
     O-07   O-06   O      1    20    22    21    23    43    55
     O-08   O-05   O      2    34    36    35    37    54    55
     O-09   O-13   O      2    29    29    30    31    43    55
     O-10   O-12   O      2    36    36    31    31    44    55
     O-11   O-14   O      2    38    38    39    39    53    55
     O-12   O-10   O      1    30    30    30    31    48    55
     O-13   O-09   O      1    31    31    27    27    52    55
     O-14   O-11   O      1    49    49    51    52    53    55
;

proc print data=cluster;
run;

############################################################
#
#          code for last BP controlled
#
############################################################

############################################################
#
#          cluster-level unweighted logistic regression
#
############################################################

proc genmod data=cluster descending;
class center assigned/desc;
model last_bpimproved/N=assigned /dist=bin link=logit pscale;
run;

proc genmod data=cluster descending;
class center assigned/desc;
model last_bpimproved/N=assigned center/dist=bin link=logit pscale;
run;

############################################################
```

```
#
#           cluster-level weighted logistic regression
#
#############################################################

data cluster_wt;
set cluster;
wt=1/(1/last_bpimproved+1/(N-last_bpimproved));
run;



proc genmod data=cluster_wt descending;
class center assigned /desc;
model last_bpimproved/N=assigned /dist=bin link=logit pscale;
weight wt;
run;


proc genmod data=cluster_wt descending;
class center assigned /desc;
model last_bpimproved/N=assigned center/dist=bin link=logit pscale;
weight wt;
run;


data cluster_wt_ajust;
set cluster;
wt=1/((1/last_bpimproved+1/(N-last_bpimproved))*(1+54*0.0766553091));
run;



proc genmod data=cluster_wt_ajust descending;
class center assigned /desc;
model last_bpimproved/N=assigned /dist=bin link=logit pscale;
weight wt;
run;


proc genmod data=cluster_wt_adjust descending;
class center assigned /desc;
model last_bpimproved/N=assigned center/dist=bin link=logit pscale;
weight wt;
run;



#############################################################
#
#           cluster-level random effect meta regression
#
#############################################################


data meta_last_bp;
input pairnum last_bp_1 last_bp_2 center $;
N=55;
logor=log((last_bp_2*(N-last_bp_1))/(last_bp_1*(N-last_bp_2)));
varlogor=1/last_bp_1+1/(N-last_bp_1)+1/last_bp_2+1/(N-last_bp_2);
datalines;
1   15   36   H
2   19   24   H
3   24   24   H
4   48   33   H
```

```
5   29   24   H
6   20   27   H
7   27   34   H
8   39   25   O
9   20   36   O
10  39   35   O
11  21   36   O
12  27   30   O
13  30   31   O
14  51   39   O
;
run;

proc print data=meta_last_bp;
run;


proc mixed data=meta_last_bp method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.17208)(0.15433)(0.14785)(0.23945)(0.14687)(0.15132)(0.14978)
(0.16147)(0.15898)(0.16671)(0.15744)(0.14608)(0.14726)(0.35775)
/ eqcons=2 to 15;
run;



data meta_last_bp_adjust;
input pairnum last_bp_1 last_bp_2 center $;
N=55;
logor=log((last_bp_2*(N-last_bp_1))/(last_bp_1*(N-last_bp_2)));
varlogor=(1/last_bp_1+1/(N-last_bp_1)+1/last_bp_2+1/(N-last_bp_2))*(1+54*0.0766553091);
datalines;
1   15   36   H
2   19   24   H
3   24   24   H
4   48   33   H
5   29   24   H
6   20   27   H
7   27   34   H
8   39   25   O
9   20   36   O
10  39   35   O
11  21   36   O
12  27   30   O
13  30   31   O
14  51   39   O
;
run;

proc print data=meta_last_bp_adjust;
run;


proc mixed data=meta_last_bp_adjust method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.88437)(0.79318)(0.75986)(1.23062)(0.75482)(0.77771)(0.76979)
(0.82988)(0.81706)(0.85680)(0.80915)(0.75079)(0.75682)(1.83861)
```

```
/ eqcons=2 to 15;
run;


############################################################
#
#          code for last systolic BP controlled
#
############################################################


############################################################
#
#          Systolic BP: Cluster-level unweighted logistic regression
#
############################################################


proc genmod data=cluster descending;
class center assigned/desc;
model last_sysimproved/N=assigned /dist=bin link=logit pscale;
run;


proc genmod data=cluster descending;
class center assigned/desc;
model last_sysimproved/N=assigned center/dist=bin link=logit pscale;
run;


############################################################
#
#            Systolic BP: Cluster-level weighted logistic regression
#
############################################################

data cluster_syswt;
set cluster;
wt=1/(1/last_sysimproved+1/(N-last_sysimproved));
run;


proc genmod data=cluster_syswt descending;
class center assigned /desc;
model last_sysimproved/N=assigned /dist=bin link=logit pscale;
weight wt;
run;


proc genmod data=cluster_syswt descending;
class center assigned /desc;
model last_sysimproved/N=assigned center/dist=bin link=logit pscale;
weight wt;
run;


############################################################
#
#          Systolic BP: Cluster-level random effect meta regression
```

```
#
############################################################


data meta_last_sys;
input pairnum last_sys_1 last_sys_2 center $;
N=55;
logor=log((last_sys_2*(N-last_sys_1))/(last_sys_1*(N-last_sys_2)));
varlogor=1/last_sys_1+1/(N-last_sys_1)+1/last_sys_2+1/(N-last_sys_2);
datalines;
1   16   36   H
2   19   24   H
3   24   25   H
4   48   33   H
5   30   24   H
6   20   27   H
7   28   34   H
8   40   25   O
9   20   36   O
10  39   37   O
11  23   37   O
12  27   31   O
13  31   31   O
14  52   39   O
;
run;

proc print data=meta_last_sys;
run;


proc mixed data=meta_last_sys method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.16855)(0.15433)(0.14726)(0.23945)(0.14726)(0.15132)(0.14978)
(0.16500)(0.15898)(0.17072)(0.15731)(0.14668)(0.14785)(0.44071)
/ eqcons=2 to 15;
run;


data meta_last_sys_adjust;
input pairnum last_sys_1 last_sys_2 center $;
N=55;
logor=log((last_sys_2*(N-last_sys_1))/(last_sys_1*(N-last_sys_2)));
varlogor=(1/last_sys_1+1/(N-last_sys_1)+1/last_sys_2+1/(N-last_sys_2))*(1+54*0.0766553091);
datalines;
1   16   36   H
2   19   24   H
3   24   25   H
4   48   33   H
5   30   24   H
6   20   27   H
7   28   34   H
8   40   25   O
9   20   36   O
10  39   37   O
11  23   37   O
12  27   31   O
13  31   31   O
14  52   39   O
;
run;
```

```
proc print data=meta_last_sys_adjust;
var varlogor;
run;


proc mixed data=meta_last_sys_adjust method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.86625) (0.79318) (0.75682) (1.23062) (0.75682) (0.77771) (0.76979)
(0.84800) (0.81706) (0.87741) (0.80848) (0.75382) (0.75986) (2.26495)
/ eqcons=2 to 15;
run;


############################################################
#
#          code for average BP controlled
#
############################################################


############################################################
#
#          Cluster-level unweighted logistic regression
#
############################################################


proc genmod data=cluster descending;
class center assigned/desc;
model ave_bpimproved/N=assigned /dist=bin link=logit pscale;
run;



proc genmod data=cluster descending;
class center assigned/desc;
model ave_bpimproved/N=assigned center/dist=bin link=logit pscale;
run;



############################################################
#
#            Cluster-level weighted logistic regression
#
############################################################

data cluster_wt;
set cluster;
wt=1/(1/ave_bpimproved+1/(N-ave_bpimproved));
run;


proc genmod data=cluster_wt descending;
class center assigned /desc;
model ave_bpimproved/N=assigned /dist=bin link=logit pscale;
weight wt;
run;
```

```
proc genmod data=cluster_wt descending;
class center assigned /desc;
model ave_bpimproved/N=assigned center/dist=bin link=logit pscale;
weight wt;
run;


#################################################################
#
#               Cluster-level random effect meta regression
#
#################################################################


data meta_ave_bp;
input pairnum ave_bp_1 ave_bp_2 center $;
N=55;
logor=log((ave_bp_2*(N-ave_bp_1))/(ave_bp_1*(N-ave_bp_2)));
varlogor=1/ave_bp_1+1/(N-ave_bp_1)+1/ave_bp_2+1/(N-ave_bp_2);
varlogor_adjust=(1/ave_bp_1+1/(N-ave_bp_1)+1/ave_bp_2+1/(N-ave_bp_2))*(1+54*0.0766553091);
datalines;
1   11   32   H
2   20   22   H
3   26   22   H
4   46   25   H
5   28   20   H
6   21   25   H
7   22   34   H
8   39   23   O
9   18   33   O
10  41   34   O
11  20   35   O
12  31   29   O
13  30   36   O
14  49   38   O
;
run;

proc print data=meta_ave_bp;
var varlogor_adjust;
run;


proc mixed data=meta_ave_bp method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.18836) (0.15433) (0.14870) (0.20618) (0.15132) (0.15036) (0.15279)
(0.16287) (0.15834) (0.17285) (0.15714) (0.14687) (0.15374) (0.27221)
/ eqcons=2 to 15;
run;


proc mixed data=meta_ave_bp method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.96808) (0.79316) (0.76424) (1.05966) (0.77771) (0.77278) (0.78524)
(0.83705) (0.81377) (0.88834) (0.80762) (0.75482) (0.79014) (1.39901)
/ eqcons=2 to 15;
run;
```

```
#####################################################
#
#          code for ave systolic BP controlled
#
#####################################################


#############################################################
#
#Systolic BP: Cluster-level unweighted logistic regression
#
#############################################################


proc genmod data=cluster descending;
class center assigned/desc;
model ave_sysimproved/N=assigned /dist=bin link=logit pscale;
run;


proc genmod data=cluster descending;
class center assigned/desc;
model ave_sysimproved/N=assigned center/dist=bin link=logit pscale;
run;



#############################################################
#
#             Systolic BP: Cluster-level weighted logistic regression
#
#############################################################

data cluster_syswt;
set cluster;
wt=1/(1/ave_sysimproved+1/(N-ave_sysimproved));
run;


proc genmod data=cluster_syswt descending;
class center assigned /desc;
model ave_sysimproved/N=assigned /dist=bin link=logit pscale;
weight wt;
run;


proc genmod data=cluster_syswt descending;
class center assigned /desc;
model ave_sysimproved/N=assigned center/dist=bin link=logit pscale;
weight wt;
run;



#############################################################
#
#        Systolic BP: Cluster-level random effect meta regression
#
#############################################################


data meta_ave_sys;
input pairnum ave_sys_1 ave_sys_2 center $;
N=55;
```

```
logor=log((ave_sys_2*(N-ave_sys_1))/(ave_sys_1*(N-ave_sys_2)));
varlogor=1/ave_sys_1+1/(N-ave_sys_1)+1/ave_sys_2+1/(N-ave_sys_2);
varlogor_adjust=(1/ave_sys_1+1/(N-ave_sys_1)+1/ave_sys_2+1/(N-ave_sys_2))*(1+54*0.0766553091);
datalines;
1   11   32   H
2   20   22   H
3   26   23   H
4   46   25   H
5   28   20   H
6   21   25   H
7   22   34   H
8   40   24   O
9   18   33   O
10  41   36   O
11  22   35   O
12  31   29   O
13  30   36   O
14  49   38   O
;

proc print data=meta_ave_sys;
var varlogor_adjust;
run;


proc mixed data=meta_ave_sys method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.18836) (0.15433) (0.14767) (0.20618) (0.15132) (0.15036) (0.15279)
(0.16559) (0.15834) (0.17623) (0.15433) (0.14687) (0.15374) (0.27221)
/ eqcons=2 to 15;
run;



proc mixed data=meta_ave_sys method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.96808) (0.79316) (0.75895) (1.05966) (0.77771) (0.77278) (0.78524)
(0.85104) (0.81377) (0.90570) (0.79316) (0.75482) (0.79014) (1.39901)
/ eqcons=2 to 15;
run;
```

F7. SAS Codes for Individual-Level Analysis of Primary Outcomes

```
#####################################################################
#
#          prepare individual-level analysis
#
#####################################################################


data chatnew;
set chat.chatmerge;
if (diabbase=8 or diabbase=9) then diabbase=0;
if (strokebase=8 or strokebase=9) then strokebase=0;
if (hypstat=8 or hypstat=9) then hypstat=0;
if (hdbase=8 or hdbase=9) then hdbase=0;
```

```
if (nephrobase=8 or nephrobase=9) then nephrobase=0;
if (pvdbase=8 or pvdbase=9) then pvdbase=0;
if (retinobase=8 or retinobase=9) then retinobase=0;
run;


#############################################################
#
#          code for last BP controlled
#
#############################################################


#############################################################
#
#                    Individual-level standard logistic regression
#
#############################################################


proc genmod data=chatnew descending;
class assigned /desc;
model last_bpimproved=assigned /D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned hypstat diabbase hdbase strokebase sex base_bpcontrolled retinobase nephrobase pvdbase/desc;
model last_bpimproved=assigned hypstat diabbase hdbase strokebase base_bpcontrolled retinobase pvdbase
        nephrobase/D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned diabbase hdbase base_bpcontrolled/desc;
model last_bpimproved=assigned diabbase hdbase base_bpcontrolled/D=B link=logit;
run;



#############################################################
#
#                    Individual-level robust standard errors
#
#############################################################


proc genmod data=chatnew descending;
class assigned assfpid / desc;
model last_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=ind;
run;


proc genmod data=chatnew descending;
class assfpid assigned diabbase hdbase base_bpcontrolled/desc;
model last_bpimproved=assigned diabbase hdbase base_bpcontrolled/D=B link=logit;
repeated subject=assfpid/type=ind;
run;



#############################################################
#
```

```
#                    Individual-level GEE
#
############################################################


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid diabbase hdbase base_bpcontrolled /desc;
model last_bpimproved=assigned diabbase hdbase base_bpcontrolled/D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model last_bpimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=unstr;
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model last_bpimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=unstr;
run;



############################################################
#
#          Individual random effects logistic regression
#
############################################################

data temp;
set chatnew;
n=1;
run;


%glimmix(data=temp, stmts=%str(
class assigned assfpid;
model last_bpimproved/n=assigned /solution;
```

```
random assfpid;
))


%glimmix(data=temp, stmts=%str(
class assigned assfpid diabbase hdbase base_bpcontrolled;
model last_bpimproved/n=assigned diabbase hdbase base_bpcontrolled/solution;
random assfpid;
))

#############################################################
#
#          code for last systolic BP controlled
#
#############################################################

#############################################################
#
#          Systolic BP: Individual-level standard logistic regression
#
#############################################################



proc genmod data=chatnew descending;
class assigned /desc;
model last_sysimproved=assigned /D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned hypstat diabbase hdbase strokebase sex base_syscontrolled retinobase nephrobase pvdbase/desc;
model last_sysimproved=assigned hypstat diabbase hdbase strokebase base_syscontrolled retinobase pvdbase
          nephrobase/D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned hdbase diabbase base_syscontrolled/desc;
model last_sysimproved=assigned diabbase hdbase base_syscontrolled/D=B link=logit;
run;



#############################################################
#
#          Systolic BP: Individual-level robust standard errors
#
#############################################################


proc genmod data=chatnew descending;
class assigned assfpid / desc;
model last_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=ind;
run;


proc genmod data=chatnew descending;
class assfpid assigned diabbase hdbase base_syscontrolled/desc;
model last_sysimproved=assigned diabbase hdbase base_syscontrolled/D=B link=logit;
repeated subject=assfpid/type=ind;
run;
```

```
#############################################################
#
#          Systolic BP: Individual-level GEE
#
#############################################################


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid diabbase hdbase base_syscontrolled /desc;
model last_sysimproved=assigned diabbase hdbase base_syscontrolled/D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model last_sysimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model last_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=unstr;
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model last_sysimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=unstr;
run;



#############################################################
#
#        Systolic BP: Individual random effects logistic regression
#
#############################################################

data temp;
set chatnew;
n=1;
run;
```

```
%glimmix(data=temp, stmts=%str(
class assigned assfpid;
model last_sysimproved/n=assigned /solution;
random assfpid;
))

%glimmix(data=temp, stmts=%str(
class assigned assfpid diabbase hdbase base_syscontrolled;
model last_sysimproved/n=assigned diabbase hdbase base_syscontrolled/solution;
random assfpid;
))

############################################################
#
#          code for average BP controlled
#
############################################################

############################################################
#
#                Individual-level standard logistic regression
#
############################################################

proc genmod data=chatnew descending;
class assigned /desc;
model ave_bpimproved=assigned /D=B link=logit;
run;

proc genmod data=chatnew descending;
class assigned hypstat diabbase hdbase strokebase sex base_bpcontrolled retinobase nephrobase pvdbase/desc;
model ave_bpimproved=assigned hypstat diabbase hdbase strokebase base_bpcontrolled retinobase pvdbase
          nephrobase/D=B link=logit;
run;

proc genmod data=chatnew descending;
class assigned diabbase hdbase ave_base_bpcontrolled/desc;
model ave_bpimproved=assigned diabbase hdbase ave_base_bpcontrolled/D=B link=logit;
run;

############################################################
#
#                        Individual-level robust standard errors
#
############################################################

proc genmod data=chatnew descending;
class assigned assfpid / desc;
model ave_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=ind;
run;

proc genmod data=chatnew descending;
```

```
class assfpid assigned diabbase hdbase ave_base_bpcontrolled/desc;
model ave_bpimproved=assigned diabbase hdbase ave_base_bpcontrolled/D=B link=logit;
repeated subject=assfpid/type=ind;
run;


############################################################
#
#                    Individual-level GEE
#
############################################################


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=exch;
run;


proc genmod data=chatnew descending;
class assigned assfpid diabbase hdbase ave_base_bpcontrolled /desc;
model ave_bpimproved=assigned diabbase hdbase ave_base_bpcontrolled/D=B link=logit;
repeated subject=assfpid/type=exch;
run;


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model ave_bpimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_bpimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=unstr;
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model ave_bpimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=unstr;
run;


############################################################
#
#          Individual random effects logistic regression
#
############################################################
```

```
data temp;
set chatnew;
n=1;
run;


%glimmix(data=temp, stmts=%str(
class assigned assfpid;
model ave_bpimproved/n=assigned /solution;
random assfpid;
))


%glimmix(data=temp, stmts=%str(
class assigned assfpid diabbase hdbase ave_base_bpcontrolled;
model ave_bpimproved/n=assigned diabbase hdbase ave_base_bpcontrolled/solution;
random assfpid;
))


############################################################
#
#          code for ave systolic BP controlled
#
############################################################

############################################################
#
#              average Systolic BP: Individual-level standard logistic regression
#
############################################################


proc genmod data=chatnew descending;
class assigned /desc;
model ave_sysimproved=assigned /D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned hypstat diabbase hdbase strokebase sex ave_base_syscontrolled retinobase nephrobase
          pvdbase/desc;
model ave_sysimproved=assigned hypstat diabbase hdbase strokebase base_syscontrolled retinobase pvdbase
          nephrobase/D=B link=logit;
run;


proc genmod data=chatnew descending;
class assigned diabbase hdbase base_syscontrolled/desc;
model ave_sysimproved=assigned diabbase hdbase ave_base_syscontrolled/D=B link=logit;
run;



############################################################
#
#                Systolic BP: Individual-level robust standard errors
#
############################################################


proc genmod data=chatnew descending;
class assigned assfpid / desc;
```

```
model ave_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=ind;
run;


proc genmod data=chatnew descending;
class assfpid assigned diabbase hdbase ave_base_syscontrolled/desc;
model ave_sysimproved=assigned diabbase hdbase ave_base_syscontrolled/D=B link=logit;
repeated subject=assfpid/type=ind;
run;


############################################################
#
#                    Systolic BP: Individual-level GEE
#
############################################################


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid diabbase hdbase ave_base_syscontrolled /desc;
model ave_sysimproved=assigned diabbase hdbase ave_base_syscontrolled/D=B link=logit;
repeated subject=assfpid/type=exch;
run;



proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model ave_sysimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=AR(1);
run;


proc genmod data=chatnew descending;
class assigned assfpid /desc;
model ave_sysimproved=assigned /D=B link=logit;
repeated subject=assfpid/type=unstr;
run;


proc genmod data=chatnew descending;
class assigned assfpid hypstat diabbase hdbase strokebase sex /desc;
model ave_sysimproved=assigned hypstat diabbase hdbase strokebase sex age/D=B link=logit;
repeated subject=assfpid/type=unstr;
run;
```

```
############################################################
#
#       Average Systolic BP: Individual random effects logistic regression
#
############################################################

data temp;
set chatnew;
n=1;
run;


%glimmix(data=temp, stmts=%str(
class assigned assfpid;
model ave_sysimproved/n=assigned /solution;
random assfpid;
))


%glimmix(data=temp, stmts=%str(
class assigned assfpid diabbase hdbase ave_base_syscontrolled;
model ave_sysimproved/n=assigned diabbase hdbase ave_base_syscontrolled/solution;
random assfpid;
))
```

F8. SAS Codes for Analysis of Secondary Outcomes

```
############################################################
#
#       secondary outcome analysis: BP monitored
#       (cluster-level analysis, random effect meta analysis)
#
############################################################

proc sql;
select trim(assfpid), sum(bpmonitored) as num_monitored, 55-sum(bpmonitored) as num_unmonitored
from chat.chatmerge
group by assfpid;


data chat.meta_bpmonitored;
input pairnum inter_monitored control_monitored;
N=55;
logor=log((inter_monitored*(N-control_monitored))/(control_monitored*(N-inter_monitored)));
varlogor=1/inter_monitored+1/(N-inter_monitored)+1/control_monitored+1/(N-control_monitored);
datalines;
1   41   50
2   40   45
3   44   39
4   51   41
5   39   41
6   49   43
7   44   49
8   51   39
9   40   46
10  52   54
11  43   45
12  48   44
13  52   43
14  53   53
;
run;
```

```
proc print data=chat.meta_bpmonitored;
run;

proc mixed data=chat.meta_bpmonitored method=ml;
class pairnum;
model logor= / s cl;
repeated / group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.31582)(0.21389)(0.20178)(0.36543)(0.18396)(0.29366)(0.30071)
(0.35775)(0.22452)(1.37108)(0.22881)(0.27733)(0.45915)(1.03774)
/ eqcons=2 to 15;
run;


#############################################################
#
#          secondary outcome analysis: BP monitored
#          (individual-level analysis, GEE)
#
#############################################################


proc genmod data=chat.chatmerge descending;
class assigned assfpid;
model bpmonitored=assigned /D=B link=logit;
repeated subject=assfpid/type=exch;
run;


data tmp_bpmonitored;
set chat.chatmerge;
if (hypstat~=0 and hypstat~=1) then hypstat=.;
if (diabbase~=0 and diabbase~=1) then diabbase=.;
if (hdbase~=0 and hdbase~=1) then hdbase=.;
if (strokebase~=0 and strokebase~=1) then strokebase=.;
if (sex~=1 and sex~=2) then sex=.;
if (retinobase~=0 and retinobase~=1) then retinobase=.;
if (nephrobase~=0 and nephrobase~=1) then nephrobase=.;
if (smokchg~=0 and smokchg~=1 and smokchg~=2) then smokchg=.;
if (nomedbase~=0 and nomedbase~=1) then nomedbase=.;
if (pvdbase~=0 and pvdbase~=1) then pvdbase=.;
run;

proc print data=tmp_bpmonitored;
var hypstat diabbase hdbase strokebase sex retinobase nephrobase smokchg pvdbase nomedbase;
run;

proc genmod data=tmp_bpmonitored descending;
class assigned assfpid hypstat diabbase hdbase pvdbase nomedbase smokchg;
model bpmonitored=assigned hypstat pvdbase nomedbase smokchg /D=B link=logit;
repeated subject=assfpid/type=exch;
run;


#############################################################
#
#                secondary outcome analysis: Frequency of BP monitoring
#                (individual-level analysis)
#
#############################################################

proc capability data=chat.chatmerge graphics noprint;
var monfreq;
histogram monfreq /cframe=gray
```

```
        cfill=blue;
run;


proc genmod data=chat.chatmerge;
class assigned assfpid;
model monfreq=assigned /D=poisson link=identity;
repeated subject=assfpid/type=exch;
run;

proc genmod data=chat.chatmerge;
class assigned assfpid;
model monfreq=assigned /D=poisson link=log;
repeated subject=assfpid/type=exch;
run;

proc genmod data=tmp_bpmonitored;
class assigned assfpid hypstat diabbase hdbase nomedbase sex nephrobase retinobase;
model monfreq=assigned hypstat hdbase nomedbase age nephrobase/D=poisson link=identity;
repeated subject=assfpid/type=exch;
run;

proc sql;
select sum(monfreq) as total, mean(monfreq) as average, sqrt(var(monfreq)) as se
from chat.chatmerge
where assigned='1';

proc sql;
select sum(monfreq) as total, mean(monfreq) as average, sqrt(var(monfreq)) as se
from chat.chatmerge
where assigned='2';


############################################################
#
#           secondary outcome analysis: Average BP
#           (without multiple imputation)
#           (Two sample T-test)
#
############################################################

proc sql;
create table chat.averageBP as
select trim(assfpid) as cluster, trim(assigned) as group, mean(lastsysaft) as mean_systolic,
    sqrt(var(lastsysaft)) as se_sys, var(lastsysaft) as var_sys, mean(lastdiaaft) as mean_diastolic,
    sqrt(var(lastdiaaft)) as se_dia, var(lastdiaaft) as var_dia
from chat.chatmerge
group by assfpid, assigned;


proc sql;
select trim(assigned) as group,
    mean(lastsysaft) as mean_sys_overall, sqrt(var(lastsysaft)) as se_sys_overall,
    mean(lastdiaaft) as mean_dia_overall, sqrt(var(lastdiaaft)) as se_dia_overall
from chat.chatmerge
group by assigned;


proc sql;
create table tmp1 as
select trim(assigned) as group, lastsysaft, lastdiaaft
from chat.chatmerge;
where assfpid='H-01' or assfpid='H-02';

proc glm data=tmp1;
```

```
class group;
model lastsysaft=group/solution;
run;


proc glm data=tmp2;
class group;
model lastsysaft=group/solution;
run;


proc glm data=chat.averageBP;
class group;
model mean_systolic=group;
weight var_sys;
run;


proc glm data=chat.averageBP;
class group;
model mean_diastolic=group;
weight var_dia;
run;


proc ttest data=chat.averageBP;
class group;
var mean_systolic;
run;


proc ttest data=chat.averageBP;
class group;
var mean_diastolic;
run;


proc npar1way data=chat.averageBP;
class group;
var mean_systolic;
run;


proc npar1way data=chat.averageBP;
class group;
var mean_diastolic;
run;


data chat.meta_mean_bp;
input pairnum inter_sys inter_se_sys inter_var_sys inter_dia inter_se_dia inter_var_dia contr_sys contr_se_sys
      contr_var_sys contr_dia contr_se_dia contr_var_dia;
datalines;
1 146.220 17.0873 291.976 74.8780 10.4790 109.810 133.700 16.2484 264.010 71.5400 9.7147
      94.376
2 142.650 24.4599 598.285 75.4000 10.8906 118.605 138.067 19.8956 395.836 73.3778
      10.8571 117.877
3 141.023 17.8749 319.511 75.7045 8.8254 77.887 135.179 15.6657 245.414 70.8947 13.1925
      174.043
4 126.235 8.2136 67.464 74.0784 7.2549 52.634 131.756 15.7270 247.339 75.0976 7.6151
      57.990
5 130.897 15.6269 244.200 70.7949 9.0268 81.483 139.854 23.0809 532.728 74.3171 10.9349
      119.572
6 142.041 20.1339 405.373 71.9375 11.2238 125.975 139.767 16.1729 261.564 75.1163 9.5224
      90.677
```

```
7 137.595 15.8331 250.686 73.8095 11.3809 129.524 132.667 17.4323 303.887 68.4375 7.2637
        52.762
8 128.843 16.9356 286.815 69.5686 8.4125 70.770 132.947 13.9593 194.862 74.2973 6.6117
        43.715
9 141.692 20.2448 409.850 76.9231 10.6903 114.283 131.630 17.6401 311.171 77.2889 9.6215
        92.574
10 132.231 16.4527 270.691 72.2692 9.9747 99.495 133.574 18.3299 335.985 76.2963 12.3129
        151.609
11 137.651 17.6148 310.280 79.2326 10.9801 120.564 127.837 15.9104 253.140 70.0930
        8.6707 75.182
12 134.511 16.9319 286.690 73.4894 10.9423 119.734 133.227 14.2631 203.436 75.7727
        8.8813 78.877
13 138.231 16.8111 282.612 75.6538 8.7378 76.348 130.791 16.9699 287.979 77.3953 9.3583
        87.578
14 126.264 8.5937 73.852 72.0943 6.4518 41.626 131.151 16.5115 272.631 71.0189 9.1262
        83.288
;
run;

data meta_mean_sys_dia_bp (keep= pairnum diff_sys var_sys var_sys_adjust diff_dia var_dia var_dia_adjust);
set chat.meta_mean_bp;
diff_sys=inter_sys-contr_sys;
var_sys=(inter_var_sys+contr_var_sys)/55;
var_sys_adjust=(inter_var_sys+contr_var_sys)/55*(1+54*0.0766553091);
diff_dia=inter_dia-contr_dia;
var_dia=(inter_var_dia+contr_var_dia)/55;
var_dia_adjust=(inter_var_dia+contr_var_dia)/55*(1+54*0.0766553091);
run;

proc print data=meta_mean_sys_dia_bp;
run;


proc mixed data=meta_mean_sys_dia_bp method=ml;
class pairnum;
model diff_sys= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(10.1088) (18.0749) (10.2714) (5.7237) (14.1260) (12.1261) (10.0831)
(8.7578) (13.1095) (11.0305) (10.2440) (8.9114) (10.3744) (6.2997)
/ eqcons=2 to 15;
run;


proc mixed data=meta_mean_sys_dia_bp method=ml;
class pairnum;
model diff_sys= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(51.9532) (92.8940) (52.7885) (29.4163) (72.5988) (62.3209) (51.8212)
(45.0095) (67.3746) (56.6899) (52.6479) (45.7990) (53.3180) (32.3765)
/ eqcons=2 to 15;
run;


proc mixed data=meta_mean_sys_dia_bp method=ml;
class pairnum;
model diff_dia= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(3.71247) (4.29967) (4.58055) (2.01135) (3.65555) (3.93913) (3.31429)
(2.08155) (3.76104) (4.56553) (3.55902) (3.61111) (2.98047) (2.27116)
```

```
/ eqcons=2 to 15;
run;


proc mixed data=meta_mean_sys_dia_bp method=ml;
class pairnum;
model diff_dia= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(19.0798) (22.0977) (23.5412) (10.3371) (18.7873) (20.2447) (17.0334)
(10.6979) (19.3294) (23.4640) (18.2912) (18.5589) (15.3178) (11.6724)
/ eqcons=2 to 15;
run;


#############################################################
#
#                secondary outcome analysis: Percentage of Patients with
#                BP Controlled
#
#############################################################

proc sql;
create table chat.per_bpcontrolled as
select trim(assfpid) as cluster, trim(assigned) as group, sum(last_bpimproved) as sum_bpimproved,
    sum(last_bpimproved)/55 as bp_percent,
    sum(last_bpimproved)/55*(1-sum(last_bpimproved)/55)/55 as var_bp_per,
    sqrt(sum(last_bpimproved)/55*(1-sum(last_bpimproved)/55)/55) as se_bp_per,
    1/(sum(last_bpimproved)/55*(1-sum(last_bpimproved)/55)/55) as bp_wt,
    sum(last_sysimproved) as sum_sysimproved,
    sum(last_sysimproved)/55 as sys_percent,
    sum(last_sysimproved)/55*(1-sum(last_sysimproved)/55)/55 as var_sys_per,
    sqrt(sum(last_sysimproved)/55*(1-sum(last_sysimproved)/55)/55) as se_sys_per,
    1/(sum(last_sysimproved)/55*(1-sum(last_sysimproved)/55)/55) as sys_wt
from chat.chatmerge
group by assfpid, assigned;


proc print data=chat.per_bpcontrolled;
run;

proc glm data=chat.per_bpcontrolled;
class group;
model percent=group/solution;
weight wt;
run;



data chat.meta_percent_bp;
input pairnum inter_bp inter_bp_per inter_var_bp inter_se_bp inter_bp_wt inter_sys inter_sys_per inter_var_sys
        inter_se_sys inter_sys_wt  contr_bp contr_bp_per contr_var_bp contr_se_bp contr_bp_wt  contr_sys
        contr_sys_per contr_var_sys contr_se_sys contr_sys_wt;
datalines;
1   15  0.27273  .003606311  0.060053  277.292  16  0.29091  .003750563  0.061242  266.63  36
        0.65455 .004111195 0.064119 243.238 36 0.65455 .004111195 0.064119 243.24
2   19  0.34545  .004111195  0.064119  243.238  19  0.34545  .004111195  0.064119  243.24  24
        0.43636 .004471826 0.066872 223.622 24 0.43636 .004471826 0.066872 223.62
3   24  0.43636  .004471826  0.066872  223.622  24  0.43636  .004471826  0.066872  223.62  24
        0.43636 .004471826 0.066872 223.622 25 0.45455 .004507889 0.067141 221.83
4   48  0.87273  .002019534  0.044939  495.164  48  0.87273  .002019534  0.044939  495.16  33
        0.60000 .004363636 0.066058 229.167 33 0.60000 .004363636 0.066058 229.17
```

```
5   29  0.52727  .004531931  0.067320  220.656  30  0.54545  .004507889  0.067141  221.83  24
        0.43636 .004471826 0.066872 223.622 24 0.43636 .004471826 0.066872 223.62
6   20  0.36364  .004207363  0.064864  237.679  20  0.36364  .004207363  0.064864  237.68  27
        0.49091 .004543952 0.067409 220.073 27 0.49091 .004543952 0.067409 220.07
7   27  0.49091  .004543952  0.067409  220.073  28  0.50909  .004543952  0.067409  220.07  34
        0.61818 .004291510 0.065510 233.018 34 0.61818 .004291510 0.065510 233.02
8   39  0.70909  .003750563  0.061242  266.627  40  0.72727  .003606311  0.060053  277.29  25
        0.45455 .004507889 0.067141 221.833 25 0.45455 .004507889 0.067141 221.83
9   20  0.36364  .004207363  0.064864  237.679  20  0.36364  .004207363  0.064864  237.68  36
        0.65455 .004111195 0.064119 243.238 36 0.65455 .004111195 0.064119 243.24
10  39  0.70909  .003750563  0.061242  266.627  39  0.70909  .003750563  0.061242  266.63  35
        0.63636 .004207363 0.064864 237.679 37 0.67273 .004003005 0.063269 249.81
11  21  0.38182  .004291510  0.065510  233.018  23  0.41818  .004423742  0.066511  226.05  36
        0.65455 .004111195 0.064119 243.238 37 0.67273 .004003005 0.063269 249.81
12  30  0.54545  .004507889  0.067141  221.833  31  0.56364  .004471826  0.066872  223.62  31
        0.56364 .004471826 0.066872 223.622 31 0.56364 .004471826 0.066872 223.62
13  27  0.49091  .004543952  0.067409  220.073  27  0.49091  .004543952  0.067409  220.07  30
        0.54545 .004507889 0.067141 221.833 31 0.56364 .004471826 0.066872 223.62
14  51  0.92727  .001226146  0.035016  815.564  52  0.94545  .000937641  0.030621  1066.51  39
        0.70909 .003750563 0.061242 266.627 39 0.70909 .003750563 0.061242 266.63
;
run;


data meta_per_bp_sys (keep= pairnum diff_bp var_bp var_bp_adjust diff_sys var_sys var_sys_adjust);
set chat.meta_percent_bp;
diff_bp=inter_bp_per-contr_bp_per;
var_bp=inter_var_bp+contr_var_bp;
var_bp_adjust=(inter_var_bp+contr_var_bp)*(1+54*0.0766553091);
diff_sys=inter_sys_per-contr_sys_per;
var_sys=inter_var_sys+contr_var_sys;
var_sys_adjust=(inter_var_sys+contr_var_sys)*(1+54*0.0766553091);
run;

proc print data=meta_per_bp_sys;
run;


proc mixed data=meta_per_bp_sys method=ml;
class pairnum;
model diff_bp= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.007717506) (0.008583021) (0.008943652) (0.006383170) (0.009003757) (0.008751315) (0.008835462)
(0.008258452) (0.008318558) (0.007957926) (0.008402705) (0.008979715) (0.009051841) (0.004976709)
/ eqcons=2 to 15;
run;


proc mixed data=meta_per_bp_sys method=ml;
class pairnum;
model diff_bp= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.039663) (0.044111) (0.045965) (0.032806) (0.046274) (0.044976) (0.045409)
(0.042443) (0.042752) (0.040899) (0.043185) (0.046150) (0.046521) (0.025577)
/ eqcons=2 to 15;
run;


proc mixed data=meta_per_bp_sys method=ml;
class pairnum;
```

```
model diff_sys= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.007861758) (0.008583021) (0.008979715) (0.006383170) (0.008979715) (0.008751315) (0.008835462)
(0.008114200) (0.008318558) (0.007753568) (0.008426747) (0.008943652) (0.009015778) (0.004688204)
/ eqcons=2 to 15;
run;


proc mixed data=meta_per_bp_sys method=ml;
class pairnum;
model diff_sys= / s cl;
repeated /group=pairnum;
random intercept /type=un subject=pairnum;
parms (0)
(0.040405) (0.044111) (0.046150) (0.032806) (0.046150) (0.044976) (0.045409)
(0.041702) (0.042752) (0.039849) (0.043308) (0.045965) (0.046336) (0.024094)
/ eqcons=2 to 15;
run;
```