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Joint modeling of longitudinal systolic and diastolic blood pressure measurements of hypertensive patients receiving treatment

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Hypertension is a chronic disease that has a major health problem over the centuries due to its significant contribution to the global health burden. It is also called high blood pressure, described by two measured quantities, Systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hence, joint longitudinal model was used to address how the evolution of SBP is associated with the evolution of DBP. The objective was to investigate the joint evolution and association of SBP and DBP measurements of hypertensive patients and identify the potential risk factors affecting the two end points. In this this study 354 hypertensive patients with age greater than or equal to 18 years, who were on treatment, and who had measured at least three times were included. For a close examination of the separate and joint models, first, each of the outcome was analyzed separately using the linear mixed model. Then, a joint model was considered to study the joint evolution and identify the potential risk factors affecting the two responses. The joint model results in model improvement in fit, and hence the preferred one, based on AIC criteria. Based on the joint model, sex, baseline age, and place of residence were the significant factors for the progression of blood pressure, while family history and all the interaction term except age by time did not appear significant. The result from the joint model suggested a strong association between the evolutions and a slowly increasing evolution of the association between SBP and DBP.

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1 Introduction

In practice, one is often confronted with situations in which multiple outcomes of similar or disparate types, recorded simultaneously, are measured repeatedly within each subject over time. A common situation is where longitudinal measurements on a continuous or discrete response are recorded along with a (possibly censored) time-to-event ("survival") outcome on each subject. For example, in diabetic studies patients are measured for biomarkers such as hemoglobin level until specific outcomes such as death from diabetes occur (Gebregziabher et al., 2010). Alternatively, we may also need to model two or more correlated longitudinal processes simultaneously, with a goal of understanding their association over time. For example, in many AIDS studies both viral load and CD4 are measured repeatedly over time which are known to be correlated .

In general, joint modeling is required and gives more efficient inference than separate analyses when we are interested in the association structure among the outcomes or when we are interested in drawing joint inferences about the different outcomes (Fitzmaurice et al., 2008; Molenberghs et al., 2005; Tsiatis and Davidian, 2004). The work described in this paper arose from the follow-up study of hypertensive patient. Hypertension is a chronic disease known to be a risk factor for the development of a number of disease processes. Its progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to pre mature morbidity and death if not treated properly (Giles et al., 2005). Systolic (SBP) and diastolic blood pressures (DBP) are considered important biomarkers of hypertension progression and used to diagnoses whether a person is experiencing high blood pressure or not. Modeling changes in biomarkers (SBP and DBP) over time will help us to identify factors influencing disease progression which is vital to improve patient's survival and quality of life. In the hypertension follow up study described in the next section, both SBP and DBP were measured repeatedly from each patient and the focus is to investigate changes in the two response variable over time as well as to detect characteristics associated with a more rapid progression. Thus, in addition to accounting for both intra-and inter-subject variations,a modeling approach should also account the possible correlation in the two responses to ensure valid inferences.

In the statistical literature, a number of approaches to joint modeling of multiple outcomes, where some or all of the outcomes are ascertained longitudinally, have been proposed, such as multivariate marginal models(Molenberghs et al., 2005), conditional models (Cox and Wermuth, 1992), shared parameter model (Tsiatis and Davidian, 2004), and joint random effects model (Verbeke and Molenberghs, 2009).

In this paper, we use the joint random-effects model that allow more flexible corre-

lation patterns in order to simultaneously model SBP and DBP processes (Fieuws and Verbeke, 2004; Chakraborty et al., 2003; Molenberghs et al., 2005; Fitzmaurice et al., 2008). In particular, we allow the models for the two outcomes to depend on separate random effects, which are themselves correlated. The remaining part of the paper is organized as follows. Section 2 describes the materials and methods. The basic findings of the study are presented and discussed in Section 3. Finally, concluding remarks are provided in Section 4.

2 Methodology

2.1 Data Source and Description

The data used for this study was obtained from Jimma university specialized Hospital chronic follow up clinic, located 352 km Southwest of Addis Ababa, Ethiopia. All patients aged 18 years or older and had a follow up start date between September 2011 and July 2013 with at least three visits then after were eligible for this study. A total of 354 patients meet the eligibility criteria and data on patients characteristics along with the repeated SBP and DBP were retrospectively recorded from patients' medical follow up card by trained health workers of the clinic.

Also, five potential explanatory variables were considered in this study. The descriptions of these covariates are presented in Table 1 below.

Table 1: Covariates used in the separate and joint analysis of SBP and DBP

No.	variables	values/codes
1	Sex	0=Female,1=Male
2	Age	Age of patients in years
3	Place of residence	0=Rural, 1=Urban
4	Family history	0=Yes, 1=No
5	Time	Observation time of blood pressure

Out of the total of 354 adult hypertensive patients, 173 (48.87%) were females, 180 (50.84%) of them were living in urban area (Jimma town) and 201 (56.78%) of the patients had no family history of hypertension. Mean age at the start of follow up was 50.198 years (standard deviation: 14.036 years) and average baseline SBP and DBP was 140.904 and 89.209 per mmHG with standard deviation of 18.583 and 12.727, respectively.

The longitudinal responses, SBP and DBP, were measured at irregular time interval with one, two or three months gap. Figure 1 shows individual profile plots of SBP and DBP along with average profile using loess smoothing.

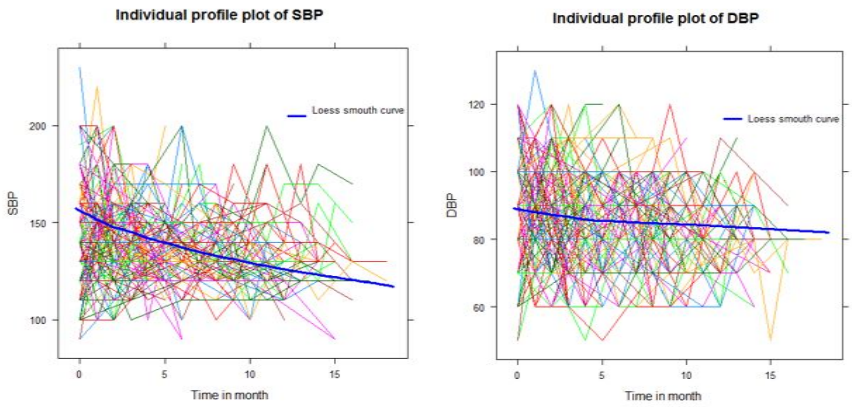

Figure 1: Individual profile plots of SBP and DBP along with average profile using loess smoothing

The variability of SBP between individuals seems higher at baseline and appears to decrease over time. Similarly, there is a between and within subjects variabilities in DBP, both implying that the between and within subject specific differences cannot be ignored. Further, The loess smooth in both plots suggest that the average profiles, the SBP and DBP, have linear relationships over time which are decreasing, but with different evolution over time.

2.2 Statistical Methods of Data Analysis

2.2.1 A model for longitudinal continuous data

Linear mixed model often used in the literature for modeling a longitudinal Gaussian outcome and provides a general and flexible modeling framework based on a random-effects approach (Laird and Ware, 1982; Molenberghs et al., 2005)

Suppose a sequence of the longitudinal measurements $\{y_{ij}, i = 1, ..., N; j = 1, ..., n_i\}$, where y_{ij} is the j^{th} observation from the i^{th} subject at times t_{ij}, were recorded.Then the Linear mixed effects model can be specified as

$$\begin{aligned} Y_i(t) &= \mu_i(t) + W_i(t) + \epsilon_i(t) \\ &= X_i(t)\beta + Z_i(t)b_i + \varepsilon_i \\ \varepsilon_i &\sim N(0, \Sigma_i) \\ b_i &\sim N(0, G) \end{aligned} \tag{1}$$

where $Y_i(t)$ is an $n_i \times 1$ dimensional vector of observed responses, β is a $p-$ dimensional vector of fixed effects, b_i is a $q-$ dimensional vector of random effects, $X_i(t)$ is a design matrix of size $n_i \times p$ associated with fixed effects possibly time-varying covariates, $Z_i(t)$ is a design matrix of size $n_i \times q$ associated with the random effects, and ε_i is an $n_i \times 1$ dimensional vector of within group errors with a Gaussian distribution.

In this model, $\mu_i(t) = X_i(t)\beta$ is the mean response and $W_i(t)= Z_i(t)b_i$ incorporates random effects. The term $W_i(t)$ can be viewed as the true individual level of SBP and DBP trajectories after they have been adjusted for the overall mean trajectory and other fixed effects. The design matrix , Z_i, for the random effects is usually a subset of the design matrix for fixed effects, X_i.

Let γ denote the vector of all variance and covariance parameters and let $\theta = (\beta', \gamma')'$ be a vector of all parameters in the mixed effects model for Y_i (1). The classical approach to inference is based on estimators obtained from maximizing the marginal likelihood function (Molenberghs et al., 2005)

$$\mathrm{L}(\theta)=\prod_{i-1}^{N}\{(2\Pi)^{-\frac{n_i}{2}}|V_i(\gamma)|^{-\frac{1}{2}}exp(\frac{-1}{2}(Y_i - X_i\beta)'V_i(\gamma)^{-1}(Y_i - X_i\beta))\} \tag{2}$$

with respect to θ, where $V_i = Z_iGZ_i' + \Sigma_i$. The maximum likelihood estimator of β is obtained from miximizing (2) conditional on γ (i.e assuming α to be known) and given by (Laird and Ware, 1982; Molenberghs et al., 2005)

$$\hat{\beta}=(\sum_{i=1}^{N} X_iV^{-1}X_i)^{-1}(\sum_{i=1}^{N} X_iV^{-1}Y_i) \tag{3}$$

Similarly, the maximum likelihood estimate of γ is obtained by maximizing (2) with respect to γ, after β is replaced by (3) (Molenberghs et al., 2005)

2.2.2 A joint model for two continuous longitudinal data

Suppose a sequence of the longitudinal measurements $\{y_{ijk}, j = 1, ..., n_{ij}, i = 1, ..., N, k = 1, ..., K\}$ represent the j^{th} observation, from the i^{th} subject, for the k^{th} response variable. The linear mixed-effects model (1) for each response variable for subject i taken at time

t can be specified as:

$$Y_{1i}(t)=\mu_{1i}(t) + W_{1i}(t) + \epsilon_{1i}(t) \tag{4}$$
$$Y_{2i}(t)=\mu_{2i}(t) + W_{2i}(t) + \epsilon_{2i}(t)$$

where $W_{1i}(t)= a_{1i}+b_{1i}(t)$ and $W_{2i}(t)= a_{2i}+b_{2i}(t)$, $\mu_{1i}(t)$ and $\mu_{2i}(t)$ refer to the average evolution's, a_{1i} and a_{2i} refers to subject specific random intercepts, $b_{1i}(t)$ and $b_{2i}(t)$ slopes that describe how the subject specific profiles deviate from the average profile for the two responses, and $\varepsilon_{ki}(t), k = 1, 2$ is error terms. Both response trajectories are tied together through a joint distribution for the random effects, as

$$\begin{bmatrix} a_{1i} \\ b_{1i} \\ a_{2i} \\ b_{2i} \end{bmatrix} \sim MVN\left(\mathbf{0}, \mathbf{G}\right) \tag{5}$$

where the variance-covariance matrix for the random effects, G, has the following structure:

$$G = \begin{bmatrix} \sigma^2_{a1} & \sigma_{a1b1} & \sigma_{a1a2} & \sigma_{a1b2} \\ \sigma_{b1a1} & \sigma^2_{b1} & \sigma_{b1a2} & \sigma_{b2b1} \\ \sigma_{a2a1} & \sigma_{a2b1} & \sigma^2_{a2} & \sigma_{a2b2} \\ \sigma_{b2a1} & \sigma_{b1b2} & \sigma_{b2a2} & \sigma^2_{b2} \end{bmatrix}. \tag{6}$$

The error components for each response, which are independent of the random effects, can be taken to be uncorrelated ($\sigma_{12} = 0$) and not associated with the random effects, such that the error components are defined as,

$$\begin{bmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_1 & \sigma_{12} \\ \sigma_{21} & \sigma^2_2 \end{bmatrix}\right) \tag{7}$$

Assuming σ_{12} =0 implies that, conditional on the random-effects, both response trajectories are independent. The assumption of conditional independence could alternatively be relaxed and the random errors could be taken to be dependent by allowing for a nonzero covariance between the error components ($\sigma_{12} \neq 0$).

Special Case of Variance Covariance Matrix

Special case can now be obtained by making specific assumptions for the variance covariance matrix G. Two such specific variance-covariance structures are described in the following paragraphs, a complete independence structure and a shared-parameters structure.

Complete Independence: The two response variable could be taken to be completely

independent at any point in time, there by imposing the following structure for G :

$$G = \begin{bmatrix} \sigma^2_{a1} & \sigma_{a1b1} & 0 & 0 \\ \sigma_{b1a1} & \sigma^2_{b1} & 0 & 0 \\ 0 & 0 & \sigma^2_{a2} & \sigma_{a2b2} \\ 0 & 0 & \sigma_{b2a2} & \sigma^2_{b2} \end{bmatrix}. \tag{8}$$

Within a response variable, the random intercept and slope induce within-subject correlations in the repeated measures over time, while assuming independence between subjects. Moreover, this model assumes that the two responses are completely independent. The results for this model would be identical, in theory, to fitting two separate random-effect models.

Shared-Parameters: Now that a complete independence structure has been considered for the G matrix one may consider the other end of the spectrum where the two response variables could be taken to be completely dependent. In this case, the two responses essentially "share" the same set of random effect parameters, (intercept and slope). When two parameters are completely dependent, the correlation between them is equal to one. This occurs when the covariance between the parameters is equal to the square root of the product of their respective variances. Most notations, however, define the model with a 2×1 vector of random effects, such as:

$$\begin{bmatrix} a_i \\ b_i \end{bmatrix} \sim MVN\begin{pmatrix} \mathbf{0} & \mathbf{G} \end{pmatrix}, \text{with G} = \begin{bmatrix} \sigma^2_a & \sigma_{ba} \\ \sigma_{ab} & \sigma^2_b \end{bmatrix} \tag{9}$$

Clearly, the aforementioned structure imposes strong assumptions on the relationship between the two response variables. It is very unlikely that the two responses would exhibit complete dependence in the association between the random slopes and between the random intercepts.

Association of the Evolution (AE): The answer to the question how the evolution of the SBP is associated with the evolution of DBP is typically derived from the covariance matrix of the random effects. Indeed, the correlation between both evolutions (AE) is given by

$$AE = \frac{cov(b_1, b_2)}{\sqrt{var(b_1)}\sqrt{var(b_2)}} = \frac{\sigma_{b_1 b_2}}{\sqrt{\sigma^2_{b_1}}\sqrt{\sigma^2_{b_2}}} \tag{10}$$

Evolution of the Association (EA): The joint model is also shows how the association between the responses evolves over time .

$$EA = \frac{Cov(Y_{i1}(t), Y_{i2}(t))}{\sqrt{Var(Y_{i1}(t))}\sqrt{Var(Y_{i2}(t))}} = \frac{\delta_{a_1 a_2} + t\delta_{a_1 b_2} + t\delta_{a_2 b_1} + t^2\delta_{b_1 b_2} + \delta_{12}}{\sqrt{\delta_{a_1} + 2t^2\delta_{a_1 a_2} + t^2\delta^2_{b_1} + \delta^2_1}\sqrt{\delta^2_{a_2} + 2t^2\delta_{b_2 b_2} + t^2\delta^2_{b_2} + \delta^2_2}} \tag{11}$$

The smaller the measurement errors of both outcomes, the closer the marginal correlation at t=0 approximates the correlation between the random intercepts. Moreover,

when t increases the marginal correlation converges to the correlation between the random slopes. It is important to note that the covariance parameters of the random effects (together with the variances of the error components) determine the shape of the marginal correlation function.

3 Result and Discussion

3.1 Separate Analysis of Systolic and Diastolic Blood Pressure

We analyze the Jimma Hypertensive patients followup study data as introduced in Section 2, where SBP as well as DBP were measured repeatedly overtime for each patient. The two outcomes will be modeled jointly to capture association between them. But first to come up with appropriate mean and variance structure we fit separate mixed effects model for each outcome and we determine the components to be included in the joint model. In many longitudinal studies it has been noted that much of the systematic variation between subjects may be explained by covariates. Thus we consider, the candidate covariates listed in section 2 along with their interaction with time and we follow backward selection to come up with a parsimonious mean structure.

3.1.1 Selection of Fixed Effects for Systolic Blood Pressure

To select the fixed effect components of the response variable, SBP and DBP, including all covariates and interaction terms with time without considering the corresponding different random effects were fitted below:

Let SBP_{ij} denote the j^{th} systolic blood pressure of the i^{th} patient at time t_{ij}, where i indexes the subjects $i = 1, 2, ..., 354$ and j indexes the time visit for subject $i, j = 1, 2, ..., n_i$ and n_i represents the overall visits of subject i. Hence, the fixed effects model with linear time effect for SBP measurement is given by:

$$\begin{aligned}\text{SBP}_{ij} = \beta_{10}+\beta_{11}\text{Sex}_i+\beta_{12}\text{Pr}_i+ \beta_{13}\text{Fh}_i+\beta_{14}\text{A}_i +\beta_{15}\text{T}_{ij} + \beta_{16}\text{Sex}_i \times \text{T}_{ij} \\ +\beta_{17}\text{Pr}_i \times \text{T}_{ij} +\beta_{18}\text{Fh}_i \times \text{T}_{ij}+\beta_{19}\text{A}_i \times \text{T}_{ij} + \varepsilon_{ij}\end{aligned} \tag{12}$$

Thus, the insignificant terms should be removed from the model starting with the most insignificant one of which is the interaction term place of residence by time with p-value of 0.912. The model was then refitted after removing the interaction term place of residence by time and the AIC dropped from 16253.08 to 16251.09 indicating a better fit. The model was fitted again and the categorical covariate family history was still insignificant. The next step is to remove the covariate family history with the p-value of 0.902. The model was fitted again and the AIC dropped from 16251.09 to 16248.57. As recommended by (Burnham and Anderson, 1998), we compute the AIC difference. The pair wise AIC difference for the aforementioned models is in the range $3-4$, meaning, the complex models have less level of empirical support. By following the same procedure the final fixed effects model for systolic blood pressure is given by:

$$\text{SBP}_{ij} = \beta_{10}+\beta_{11}\text{Sex}_i+\beta_{12}\text{Pr}_i+\beta_{14}\text{A}_i +\beta_{15}\text{T}_{ij} + \beta_{16}\text{Sex}_i \times \text{T}_{ij} \tag{13}$$

$$+\beta_{19}\mathrm{A}_i \times \mathrm{T}_{ij} + \varepsilon_{ij}$$

Hence, in this study sex, place of residence, age, time and the interaction terms sex by time and age by time used as fixed effects in the model for systolic blood pressure.

3.1.2 Selection of Random Effects for Systolic Blood Pressure

In order to retain or remove the random effects from the model, it is better to fit the linear mixed effects model with different random effects. Thus, four different models with different random effects starting from a simple linear regression model (no random effects) have been explored. Table 2 shows summary measures: Akaki information criteria (AIC), Bayesian information criteria and Log-likelihood ratio test for the models with different random effects. An appropriate random effect to the model was selected by using AIC value. The conclusion is consistent with the AIC and the BIC values for which smaller value is considered as better. That is, the AIC information criterion decreased from 16248.57 to 15940.16, which indicates that model with intercept and slope, was a better fitting model.

Table 2: Selection of random effects to be included in the linear mixed effects model for SBP. Note that: L.slopes and Q.slopes are random effect for the liner time effect and quadratic time effect respectively

No.	Random Effects Included	AIC	BIC	Loglik
1	No Random Effects	16248.57	16309.18	-8124.301
2	Random Intercepts	16008.82	16075.66	-7992.407
3	Random Intercepts and L.Slopes	15940.16	16018.14	-7956.079
4	Random Intercepts, L. and Q. Slope	15940.90	16057.83	-7949.448

Hence, the final linear mixed effects model for SBP is given by:

$$\mathrm{SBP}_{ij} = \beta_{10}+\beta_{11}\mathrm{Sex}_i+\beta_{12}\mathrm{Pr}_i +\beta_{14}\mathrm{A}_i +\beta_{15}\mathrm{T}_{ij} + \beta_{16}\mathrm{Sex}_i \times \mathrm{T}_{ij} \tag{14}$$

$$+\beta_{19}\mathrm{A}_i \times \mathrm{T}_{ij} + w_{1i}(t_{ij}) + \varepsilon_{ij}$$

where, $w_{1i}(t_{ij})$=a_{10}+b_{11}*T_{ij}. Here, $w_{1i}(t_{ij})$ includes the random effects for intercept and linear time slopes, where the b_1=$(a_{10}, b_{11}) \sim MVN(\mathbf{0}, \mathbf{G})$. The vector $(\beta_{10}, \beta_{11}, ...\beta_{1p})$ of fixed effects describes the average evolution of SBP and the vector (a_{10}, b_{11}) of random effects describes how the profile of the i^{th} subject deviates from the average profile.

By following the same procedure as separate analysis of SBP the final parsimonious linear mixed effects model for DBP is given by:

$$\mathrm{DBP}_{ij} = \beta_{20}+\beta_{21}\mathrm{Sex}_i+\beta_{22}\mathrm{Pr}_i+\beta_{24}\mathrm{A}_i +\beta_{25}\mathrm{T}_{ij} + \beta_{26}\mathrm{Sex}_i \times \mathrm{T}_{ij} \tag{15}$$

$$+\beta_{29}\mathrm{A}_i \times \mathrm{T}_{ij} +w_{2i}(t_{ij}) + \varepsilon_{ij}$$

where, $w_{2i}(t_{ij})$=$a_{20} + b_{21} * T_{ij}$. Here, $w_{2i}(t_{ij})$ includes the random effects for intercept and linear time slopes, where the b_2=$(a_{20}, b_{21}) \sim N(0, G)$.

Table 3: Parameter estimates and standard errors for the separate LMMs of the SBP and DBP for the final model

SBP			DBP		
Parameter	Estimate(S.e)	P-value	Parameter	Estimate	P-value
Fixed effects					
β_{10}	128.189(2.811)	0.0000	β_{20}	89.22(1.967)	0.0000
β_{11}	5.121(1.539)	0.0010	β_{21}	2.926(0.856)	0.0070
β_{12}	3.011(1.099)	0.0062	β_{22}	0.805(1.035)	0.4360
β_{14}	0.144(0.054)	0.0086	β_{24}	-0.077(0.037)	0.0390
β_{15}	-1.744(0.308)	0.0001	β_{25}	-1.093(0.465)	0.0191
β_{16}	-0.799(0.248)	0.0013	β_{26}	-0.081(0.176)	0.0380
β_{19}	-0.011(0.009)	0.0300	β_{29}	-0.024(0.005)	0.0001
Random effects					
Var($\hat{a}_{10}$)	130.09(15.124)		Var($\hat{a}_{20}$)	133.16(15.036)	
Var($\hat{b}_{11}$)	1.775(0.366)		Var($\hat{b}_{21}$)	2.010(0.357)	
δ_1^2	149.28(5.684)		δ_1^2	147.53(5.613)	

3.2 Joint Analysis of SBP and DBP

The joint linear mixed-effects model (4) was used to fit the two response variables, DBP and SBP, assuming an unstructured variance-covariance structure as discussed is Section 2.2.2. This model is the same as the separate model discussed in the previous section, except the sets of random intercepts and slopes for each response are now correlated rather than independent. This model was fitted allowing for a linear time effect for each covariate and by considering all covariates as a fixed effect with all possible interaction terms.

The interaction term sex by time and age by time are significant for both SBP and DBP. Thus, the insignificant terms should be removed from the model and refitted after removing the insignificant terms, the AIC value dropped from 30865.4 to 30694.6 indicating a better fit, which is the final joint model.

Table 4: Parameter estimates, standard errors (s.e) and 95% confidence intervals (CI) for the joint linear mixed effects model of the SBP and DBP outcomes for the final model.

	SBP		DBP	
Effect	Estimate(s.e)	95% CI	Estimate(s.e)	95% CI
Intercept	128.46(2.801)	(122.98, 134.12)*	89.391(1.965)	(85.53, 93.27)*
Sex:Male	5.148(1.540)	(2.165, 8.262)*	3.053(1.074)	(0.941, 5.164)*
Pr:Rural	3.014(1.103)	(0.444, 4.785)*	0.323(0.826)	(-1.302, 1.948)
Age	0.140(0.055)	(0.032, 0.248)*	-0.078(0.038)	(-0.153, -0.003)*
Time	-1.797(0.317)	(-2.424, -1.171)*	-1.097(0.455)	(-1.990, -0.205)*
Sex:Male×T	-0.809(0.250)	(-1.319, 0.294)	-0.048(0.167)	(-0.378, 0.285)
Age×T	- 0.011(0.008)	(-0.025, -0.0024)*	-0.025(0.006)	(-0.033, -0.012)*

All the parameters were found significant at 5 percent level of significance except the interaction term sex by time for SBP and place of residence and the interaction term sex by time for DBP. The variable sex, place of residence and age are identified as positively associated with change in SBP, but time is negatively associated with SBP. Sex is the only variable which is identified as a positive risk factor for the change in DBP, but time and age are negatively associated with the change in DBP. The intercept 128.46 and 89.391 with standard error of 2.801 and 1.965 represent estimates of the average level of SBP and DBP during the first follow up time, respectively. The parameter estimates 5.148 and 3.053 for SBP and DBP respectively, indicate that on average males started with the higher SBP and DBP measures than females at baseline. The average intercept 3.014, which indicate that on average hypertensive patients living in rural area started with the higher SBP measure than living in urban area at baseline. A parameter estimate of age for both SBP and DBP indicates a one year increase in age was associated with a normal increase of 0.140 mmHG (s.e = 0.055) in SBP and a normal decrease of 0.078 mmHG (s.e =0.038) in DBP. The parameter estimate of the interaction for age and time is 0.014 and 0.025 for SBP and DBP, respectively, which implies that the average rate of increase is inversely related to age. A unit increase in time was associated with 1.797 rate of decreasing on SBP and 1.097 rate of decreasing on DBP.

Accordingly, the SAS PROC MIXED for joint model also provides the estimated variance covariance matrix, and the estimated correlation matrix for random effects of both the SBP and the DBP are shown in Table 5 and Table 6, respectively.

Table 5: Variance-Covariance estimates for the final joint model

		SBP		DBP	
		Intercept	Slope	Intercept	Slope
SBP	Intercept	133.16	-11.5415	76.3829	6.2179
	Slope	-11.5415	2.0101	6.5604	0.8112
DBP	Intercept	76.3829	6.5604	55.3012	-2.8417
	slope	6.2179	0.8112	-2.8417	0.4827

Table 6: Estimated correlation matrix:

		SBP		DBP	
		Intercept	Slope	Intercept	Slope
SBP	Intercept	1.0000	-0.7054	0.8901	0.7756
	Slope	-0.7054	1.0000	0.6222	0.8236
DBP	Intercept	0.8901	0.6222	1.0000	-0.5500
	slope	0.7756	0.8236	-0.5500	1.0000

From the random effects estimate, it can be seen that variability is higher for SBP (random slope = 2.0101) than DBP (random slope = 0.4827) which is inline with the recommendation adopted by the WHO and ISSHP (Davey and MacGillivray, 1988) which states that SBP is more variable than DBP. On the other hand, we found a high correlation between the random intercept for the SBP and DBP, meaning that a patient with an initial SBP higher than average is likely to have an initial DBP which is also higher than average (Molenberghs et al., 2005). With joint mixed-effects model, it is possible to investigate how the evolution of DBP is associated with the evolution of SBP, the association of the evolutions (AE). It is also possible to determine how the association between DBP and SBP evolves over time, the evolution of the association (EA). The AE can be determined by using equation (10) from Section 2.2.2 or by reading the correlation between the two slopes directly from the estimated correlation matrix (Table 6). Here the AE between the random slope for DBP and the random slope for SBP is 0.8236. Thus, the larger positive value suggests a positive strong association between the evolution of systolic and diastolic blood pressures.

The EA can be determined, and then visualized, using the marginal correlation between DBP and SBP, equation (11) from Section 2.2.2. To visualize this, the implied correlation has been calculated and plotted over time using the marginal correlation between both response variables in Figure 2. Notice that its weakest correlation is 0.0075, at baseline, and this association slightly increases over time.

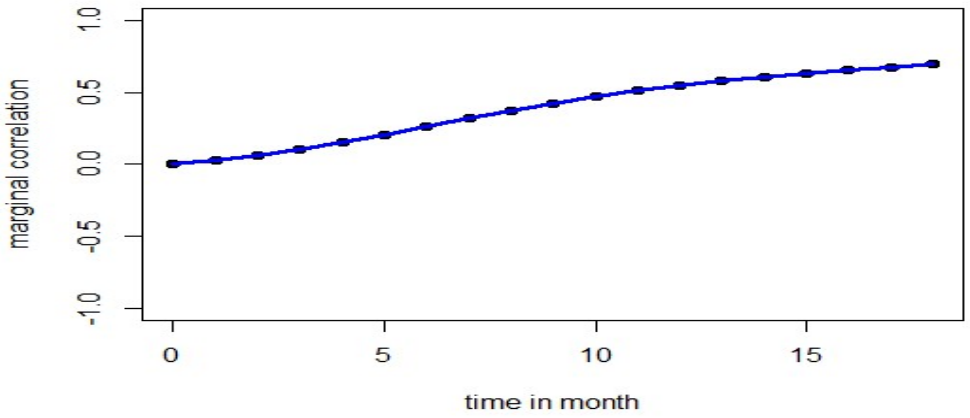

Figure 2: Associations of the Evolution

3.3 Comparison of Separate and Joint Model

Technically, the separate models were fitted for the two outcomes together anyway, but assuming that $\rho = 0$ (fit as a joint model with appropriate covariance terms equal to zero), which is entirely equivalent to fitting the models separately, using SAS PROC NLMIXED for both separate and joint model provides the following results.

In general, both models provide similar results for the fixed effect parameter estimates and their associated standard error. However, the etimates for the random effect components obtained from the separte model is slightly lower than for the joint model while the estimates for the residual variance is higher than the joint model. SBP and DBP show a strong direct relationship as evidenced by the correlation of the random effects in the joint model.With regards to AIC and -2log-likelihood, the joint model fitted the data better than the separate model.

4 Conclusion

In this study two methods were considered for fitting two response variables measured longitudinally. Based on separate analysis; the evolution of SBP and DBP measures were significantly differ with respect to time, sex, baseline age and time interaction with sex and age of hypertensive patients. Moreover, on average SBP and DBP measure decreases in a linear pattern over time after patients initiated anti- hypertensive drugs.

In joint analysis sex, baseline age and place of residence were identified as positive

risk factors for the change in SBP, but time is negatively associated with SBP. Sex is the only variable which is identified as a positive risk factor for the change in DBP, but time and baseline age are negatively associated with the change in DBP. The presence of family history did not have any association on the change of both SBP and DBP.

The result shows, the joint model has a very smaller AIC value which indicates that it fits the data better than the separate model. The joint model further allows us to answer questions, such as, how the association between the two outcomes evolves overtime and how outcome specific evolution are related to each other, which can not be answered by using the separate modeling approach.

Table 7: Parameter estimates and standard errorsfor separate and joint model

	Separate Model		Joint Model	
Effect	Estimate(s.e)	95% CI	Estimate(s.e)	95% CI
SBP				
Fixed Effects				
Intercept	128.19(2.814)	(122.66, 133.72)	128.46(2.801)	(122.89, 134.02)
Sex:M	5.122(1.540)	(2.093, 8.151)	5.149(1.539)	(2.102, 8.197)
Pr:Rural	3.012(1.105)	(0.837, 5.187)	3.0124(1.075)	(0.312, 5.713
Age	3.012(1.105)	(0.837, 5.187)	3.0124(1.075)	(0.312, 5.713)
Time	-1.777(0.305)	(-2.379, -1.174)	-1.797(0.317)	(-2.424, -1.171)
Sex:M×T	-0.799(0.259)	(-1.292,-0.308)	-0.809(0.257)	(-1.319, 0.293)
Age×T	-0.011(0.009)	(-0.029,-0.007)	-0.014(0.008)	(-0.028,-0.007)
Random Effects				
Var($\hat{a}_{10}$)	130.09(15.124)	(104.88, 165.68)	133.16(15.036)	(107.56, 169.18)
Var($\hat{b}_{11}$)	1.775(0.366)	(1.230, 2.786)	2.010(0.357)	(1.401, 3.126)
δ_1^2	149.28(5.684)	(138.74,161.08)	147.53(5.613)	(137.12, 159.19)
DBP				
Fixed Effects				
Intercept	89.349(1.956)	(85.502, 93.197)	89.351(1.967)	(85.482, 93.219)
Sex:M	2.842(1.068)	(0.740, 4.944)	2.858(0.853)	(1.1840, 4.533)
Pr:Rural	0.463(0.834)	(-1.177, 2.103)	0.423(0.828)	(-1.177, 2.083)
Age	0.463(0.834)	(-1.177, 2.103)	0.423(0.828)	(-1.177, 2.083)
Time	-1.093(0.468)	(-2.016, -0.170)	-1.097(0.475)	(-1.990,-0.204)
Sex:M×T	-0.079(0.177)	(-0.296, -0.041)	-0.048(0.167)	(-0.378, 0.285)
Age×T	-0.024(0.006)	(-0.036, -0.013)	-0.025(0.006)	(-0.037,-0.013)
Random Effects				
Var($\hat{a}_{20}$)	53.698(7.498)	(41.705, 71.755)	55.301(7.455)	(59.594,93.171)
Var($\hat{b}_{21}$)	0.359(0.150)	(0.182, 1.013)	0.483(0.142)	(0.267, 1.127
δ_2^2	95.179(3.625)	(88.456, 102.70)	93.936(3.575)	(9.026, 9.694)
ρ	.	.	0.824(0.199)	(0.421, 1.202)
-2log-likelihood	30820.0		30670.6	
AIC	30836.0		30694.6	

The joint model also suggested a strong association between the evolutions and a slowly increasing evolution of the association between systolic and diastolic blood pressure .

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Appendix

SAS Code for selected Mixed-Effects Models

A. PROC MIXED Codes

```
/***Separate Models***/
proc mixed data= joint covtest;
class name sex pr id;
model resp =sex pr age time time*sex pr*time time*age /solution cl
ddfm= kr;
random int time/ sub=id type = un group = name g gcorr;
repeated name/type=vc subject=id;
run;

/***Joint Model****/
proc mixed data= joint covtest;
class name sex pr id;
model resp = sex pr age time time*sex pr*time time*age /solution cl
ddfm= kr;
random name name*time / sub=id type=un g gcorr;
repeated name/type=vc group=name subject=id;
run;
```

B. PROC NLMIXED Codes

```
proc nlmixed data=joint qpoints=10;
parms beta10= 128.18903 beta11= 5.1861 beta12= 3.01194 beta14=0.14457
beta15=-1.09317 beta16=-0.79991 beta19= 0.01092 beta20= 89.218
beta21= 2.8585 beta22=0.6847 beta24= -0.07463 beta25=-1.6091 beta27=-0.1290
beta29= 0.02323 sigma1= 12.4730 sigma2= 9.8945 tau1=11.405828 rho=0.1
tau2= 1.332393 tau3= 6.2079 tau4=0.6012819;
if name = "1" then do;
mean= beta10 + beta11*sex+beta12*pr+beta14*age+beta15*time+beta16*time*sex
+beta19*time*age + a10+b11*time;
dens = -0.5*log(3.14159265358) - log(sigma1)-0.5*(resp-mean)**2/(sigma1**2);
ll = dens;
end;
if name= "2" then do; mean = beta20 + beta21*sex+beta22*pr+beta24*
age+beta25*time
+beta27*time*pr+beta29*time*age + a20+b21*time;
dens = -0.5*log(3.14159265358) - log(sigma2)-0.5*(resp-mean)
*2/(sigma2**2);
ll = dens;
end;
model resp~general(ll);


  /***Separate Model****/
random a10 b11 a20 b21 ~normal([0,0,0,0],[tau1**2,0,tau2**2,0,0,
```

```
tau3**2,0,0,0,tau4**2]) subject=id;

/***Joint Model****/
random a10 b11 a20 b21 ~normal([0,0,0,0],[tau1**2,rho*tau1*tau2,tau2**2,
rho*tau1*tau3,rho*tau2*tau3, tau3**2,rho*tau1*tau4,rho*tau2*tau4,
rho*tau3*tau4,tau4**2]) subject=id;
run;
```