Investigation of prospective longitudinal development of such pychological changes after a whiplash trauma

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Contents

Illustrations

List of Figures

List of Tables

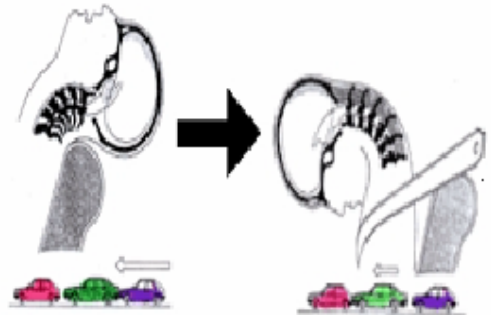
Abstract

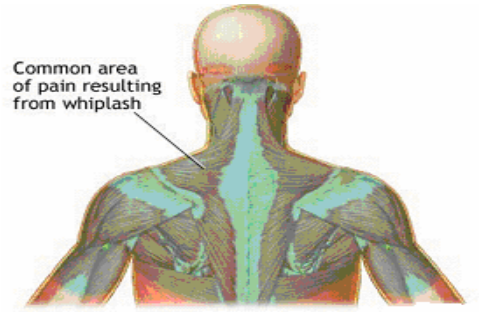
Background: Not only physical functions, but also psychological factors are more relevant to the whiplash. One way to reflect whiplash is recorded by Neck Disability Index (NDI). **Objectives:** The principal research is to investigate the association between NDI scores and the various psychological factors, social activities and working status after an injury. Also gender and age are taken into account. Furthermore, the analysis is carried out after categorizing NDI (NDIc) into two levels by mean. **Material:** The dataset includes 20 patients and all the information is recorded at week 1, week 6 and week 12 after an accident. **Methods:** Linear mixed model is fitted for the response of NDI**.** Marginal models (Generalized Estimating Equations (GEE) and Alternating Logistic Regression (ALR)) and random effect model are fitted for the response NDIc. **Results:** For the continue response of NDI, it obtains a model with a significant of Tampa Scale of Kinesiophobia (TSK), State-Trait Anxiety Inventory-Situational (STAI-S), State-Trait Anxiety Inventory -Trait (STAI-T), and the significant different evolutions for both male and female group over time. When the model takes Visual Analog Scale (VAS), physical activities (FA) and social activities (SA) into account, there are not only the significant effects by psychological factors, but also VAS, FA and SA. For the binary response of NDIc, there is only a significant effect of TSK. Following, taken FA, SA, VAS into account, there are only a significant effect of VAS and no effects of psychological factors. **Discussion and Conclusion:** Based on all the models, it implies that psychological factors act the important roles for reflecting the NDI scores. However, when the response is categorized into two levels by mean, the results cannot correctly reflect the NDI.

Keywords: *Whiplash, Linear mixed model, Marginal model, Random effect model, Neck Disability Index (NDI)*

Chapter 1 Introduction

Whiplash is a nonmedical term used to describe neck pain following an injury to the soft tissues of neck (specifically ligaments, tendons, and muscles). It occurs when a person is rear-ended in an automobile. This causes movement of the structures within the neck changing the normal curve of the upper back and neck. The sudden backward movement (extension) and forward movement (flexion) can cause the joints of the neck to be injured and can also cause the muscles and ligaments of the neck and upper back to be over-stretched. The neck is particularly vulnerable to this type of injury because of its ability to move in many directions.





The symptoms of whiplash may include neck pain, tenderness and stiffness, headache, dizziness, nausea, shoulder and/or arm pain, paresthesias (numbness/tingling), blurred vision, and in rare cases difficulty swallowing. Symptoms may appear as quickly as two hours following an injury. One way to reflect these symptoms is to be recorded by Neck Disability Index (NDI), which measures self-rated disability due to neck pain. Sterling M. and Jull G. demonstrated that both physical and psychological factors play a role in recovery or non-recovery from whiplash injury. *(Sterling M., Jull G., Physical and psychological factors predict outcome following whiplash injury, 2005, Page 114(1-2), 141-8)* It means that the NDI value was not only influenced by the physical functions, but also the psychological factors (e.g. Tampa Scale of Kinesiophobia (TSK) score, State-Trait Anxiety Inventory (STAI)) and the daily life experiences (e.g. physical and social activities, working status) after an injury.

In this paper, the principal research is to investigate the association between NDI and the various psychological factors, also social activities and working status after an injury. Gender and age are taken into account as well. Furthermore, the analysis is also carried out after categorizing NDI (NDIc) into two levels by mean.

In Section 2, it presents the basic material and methodologies (by the continues response of NDI and the binary response of NDIc) for dataset. Secondly, some descriptive statistics and explorations are presented in Section 3. Fitting linear mixed model by the continues response of NDI is discussed in Section 4.1. In addition, fitting marginal models (Section 4.2.2) and Generalized Linear Mixed Model (GLMM) (Section 4.2.3) the binary response of NDIc are given in Section 4.2. Finally, discussion and conclusion such as comparison of models by the different responses are represented in Section 5.

Chapter 2 Materials and Methods

2.1 Data Description

The dataset included 20 patients, which suffered from accidents. The continues variables were Neck Disability Index (NDI) score, Tampa Scale of Kinesiophobia (TSK) score, State-Trait Anxiety Inventory (STAI) score and Visual Analog Scale (VAS) score. The NDI score was a standard instrument for measuring self-rated disability due to neck pain. The questionnaire of NDI included 10 items, which was scored from 0 - 10. The maximum score was therefore 100. A higher score of NDI meant higher pain. The TSK score was a 17-item checklist that was developed as a measure of fear of movement/(re)injury. The total score of TSK ranged between 17 and 68. A high value on the TSK indicated a high degree of kinesiophobia. The STAI score was a self-report assessment device with the range 0-80 which included separate measures of state and trait anxiety. Higher scores on their respective scales meant more trait or state anxiety. In addition, the STAI score was defined by situation anxiety (STAI-S) and disposition anxiety (STAI-T). The Visual Analog Scale (VAS) score with range 0-100 was designed to present to the respondent a rating scale with minimum constraints. The categorical variables were the status of physical activity (FA) and social activity (SA). Both of them were defined to 4 levels. These are ordinal degrees of physical functioning, as attributed by the physiotherapist (expert opinion). Also age and gender were taken into account. Each of the interest variables was measured at week1, week 6 and week 12 after an accident. In this dataset, all the measurements had been taken from all the patients, i.e. there was no missing data problem.

2.2 Methodology for the Continues Response

In the analysis of the continues response of NDI, the correlation that existed within

subject must be taken into account. The classical techniques, which basically assumed independent measurements, might give wrong results under longitudinal set up. In this paper, linear mixed model would be fitted by *mixed* procedure in SAS software. This fitting process included fixed effects, random effects and serial correlation.

2.2.1 Fixed Effects

In the fixed effects part, the first objective was to reduce saturated model to a more parsimonious model. Reduction of mean structure was done via appropriate F-tests on various hypotheses of interest. For example, in Section 4.1.1, the saturated model could write as following:

$$\begin{aligned} Y_{ij} &= \beta_1 Age_i + \beta_2 TSK_i + \beta_3 STAIS_i + \beta_4 STAIT_i + \beta_5 Female_i + \beta_6 Male_i \\ &+ (\beta_7 Age_i + \beta_8 TSK_i + \beta_9 STAIS_i + \beta_{10} STAIT_i + \beta_{11} Female_i + \beta_{12} Male_i) t_{ij} \\ &+ (\beta_{13} Age_i + \beta_{14} TSK_i + \beta_{15} STAIS_i + \beta_{16} STAIT_i + \beta_{17} Female_i + \beta_{18} Male_i) t_{ij}^{\ 2} \\ &+ b_{1i} + b_{2i} t_{ij} + b_{3i} t_{ij}^{\ 2} + \varepsilon_{ij} \end{aligned} \quad \text{.....(2.1)}$$

Y_{ij} was the j^{th} measurement for the i^{th} patient. β_i was the vector of the fixed effects parameters. b_i was the vector of subject-specific effects and it followed the normal distribution $N(0, D)$. ε_{ij} was the vector of error components and followed normal distribution $N(0, \Sigma_i)$. Moreover, b_{1i}, b_{2i}, b_{3i} and $\varepsilon_1, \varepsilon_2 \ldots \varepsilon_i$ are independent. For example, the interest of null hypothesis could be wrote as:

$$H_0 : \begin{cases} \beta_1 = 0 & (no \quad AGE \quad effect \quad) \\ \beta_7 = 0 & (no \quad AGE \quad by \quad time \quad effect \quad) \\ \beta_{13} = 0 & (no \quad AGE \quad by \quad quadratic \quad time \quad effect \quad) \\ \beta_{14} = 0 & (no \quad TSK \quad by \quad quadratic \quad time \quad effect \quad) \\ \beta_{15} = 0 & (no \quad STAI - S \quad by \quad quadratic \quad time \quad effect \quad) \end{cases} \text{.....(2.2)}$$

This hypothesis assumed no age effects, but also no age effects with linear and quadratic time, no quadratic time effects with STAI-S and TSK. The test of this hypothesis would be carried out via *contrast* statement in the SAS software.

2.2.2 Random Effects

In the model (2.1), there was assumption which model included all random intercepts, random linear time effects and random quadratic time effects. The process of assessing the importance of the random effects would be achieved via the likelihood ratio tests, using the chi-squared mixture distributions.

After fitting random effects components, according to the likelihood ratio test used the chi-square distribution, the covariance structure should be checked. Although many structures were available, in longitudinal data analysis, one usually specified 'Unstructured' which did not assume the random-effects covariance matrix to be of any specific form. *(Verbeke G., Molenberghs G., Linear Mixed Models for Longitudinal Data, 2000, Page 98)* In this analysis, the covariance structure was selected only between 'Simple' and 'Unstructured' structure. The SAS *mixed* procedure with the option *type=simple/un* in the *random* statement was used.

2.2.3 Serial Correlation

The selection of an appropriate residual covariance structure was a nontrivial step in the model selection process, especially in the presence of random effects. *(Verbeke G., Molenberghs G., Linear Mixed Models for Longitudinal Data, 2000, Page 135)* Based on the model (2.1), it assumed that the residual component ε_{ij} could be decomposed as $\varepsilon_{ij} = \varepsilon_{(1)ij} + \varepsilon_{(2)ij}$, in which $\varepsilon_{(1)ij}$ was a component of measurement error and $\varepsilon_{(2)ij}$ was a component of serial correlation. The choice of serial correlations used in this case were the simple, the exponential and the Gaussian serial structure. The SAS *mixed* procedure with the option *type=simple/sp(exp)(time)/sp(gau)(time)* in the *repeated* statement was considered.

2.3 Methodology for the Binary Response

According to the requirement of the analysis, the NDI scores would be categorized into two levels by mean. Hence, Categorized Neck Disability Index (NDIc) as a binary response would be taken into account. The expectation of the measurements within patient in which were correlated, should be considered. Therefore, the classical methods such as logistics regression were invalid. Two models might be of the interest for this case: the marginal and the random effects models.

2.3.1Marginal Models

In marginal models, the primary scientific objective was to analyze the population average evolution of the binary responses of NDIc given the covariates. In mid-1980's, a paper appearing in the statistical literature by Liang and Zeger (1986) proposed Generalized Estimating Equations (GEE), a non likelihood approach requiring only the correct specification of the univariate marginal distributions provided one is willing to adopt incorrect structure or so called working correlation matrix. The standard Generalized Estimating Equations (GEE), which proceeded modeling of the association through marginal correlations, and the Alternating Logistic Regression (ALR), which allowed modeling of the association through marginal odds ratios.

Generalized Estimating Equations (GEE)

Due to drawbacks of AR(1) working correlation assumption, which required time points at each measurements must be equidistant. The unstructured, independent and exchangeable correlation structure were used as working correlation assumptions. In the independent working assumption the working correlation here was the unit matrix. The unstructured working assumption supposed a complex correlation structure. The exchangeable working assumption supposed that any two individuals or observations within the same patient exhibited a constant correlation. The SAS *genmod* procedure with the option *type=exch/un/ind* in the *repeated* statement was used to fit GEE.

Alternating Logistic Regression (ALR)

Unlike GEE, which merely took marginal correlation as working assumption, Alternating Logistic regression (ALR) used the odds ratio between repeated measurements as formal possibility instead of correlation. The unstructured working assumption supposed that any two measurements within the same patient exhibited different log odds ratio. The exchangeable working assumption supposed that any two individuals within the same cluster exhibited same log adds ratio. The SAS *genmod* procedure with the option *logor=fullclust/exch* in the *repeated* statement was used to fit ALR.

2.3.2 Random Effect Model

The Generalized Linear Mixed Model (GLMM)

In contrast to marginal models, the Generalized Linear Mixed Model (GLMM) was a random-effects mode. The GLMM could be represented as follows:

$$\log it(E(Y_{ij} \mid b_i) = x_{ij}^T \beta + z_{ij}^T b_i \qquad \text{.....(2.3)}$$

b_i was the random effects vector and it is assumed that b_i followed a normal distribution with mean 0 and variance D, with x_{ij}^T and z_{ij}^T p-dimensional and q-dimensional vectors of known covariates values. β was also a p-dimensional vector of unknown fixed regression coefficients. The interpretation of the parameter estimates differed from the marginal model and was conditional on the random effects b_i. The SAS *nlmixed* procedure was used to fit GLMM.

Chapter 3 Exploratory Data Analysis

3.1 Descriptive Statistics for the Continues NDI

In this case, the response was the Neck Disability Index (NDI) value. Eight important covariates were categorized as ordinal variables e.g. FA and SA, binary variables e.g. gender and continue variables e.g. age, Tampa Scale of Kinesiopobia (TSK), State-Trait Anxiety Inventory-Situational (STAI-S), State-Trait Anxiety Inventory-Trait (STAI-T) and Visual Analog Scale (VAS).

From Table 3.1, the mean of the NDI score was decreased over time as well as the mean by sex. And the trends of the average evolution by FA, SA were not clear. It would be better when the sample size of dataset was extended.

Table3.1: The descriptive of NDI by categorized variables over time

	Week 1	**Week 6**	**Week 12**
	Mean (Sd)	**Mean (Sd)**	**Mean (Sd)**
NDI	41.70 (16.24)	22.30 (15.48)	18.60 (14.77)
By SEX			
SEX=0	38.50 (4.50)	18.25 (11.34)	17.25 (13.39)
SEX=1	43.83 (20.74)	43.83 (20.74)	19.50 (16.14)
By FA			
FA=1	47.84 (15.61)	30.67 (11.02)	42.00 (.)
FA=2	30.00 (12.11)	37.00 (4.24)	40.00 (15.10)
FA=3	30.67 (11.02)	16.80 (1.10)	22.50 (10.25)
FA=4	. (.)	12.22 (8.63)	10.00 (6.77)
By SA			
SA=1	58.00 (16.64)	50.00 (7.21)	. (.)
SA=2	42.40 (6.54)	37.00 (4.24)	41.33 (15.01)
SA=3	32.00 (8.82)	20.00 (5.42)	31.00 (4.24)
SA=4	18.00 (.)	12.91 (7.87)	12.40 (9.42)

Exploring the Average Evolution

The average evolution described how the profile for a number of relevant subset evolves over time. The result of this exploration would be useful in order to choose a fixed-effects structure for the linear mixed model. *(Verbeke G., Molenberghs G., Linear Mixed Models for Longitudinal Data, 2000, Page31)*

The average evolution plot was shown in Figure 3.1. These measurements were taken about 12 weeks, from week 1 on. It displayed that the mean of NDI decreased from week 1 to week 12 as same results as Table 3.1. Moreover, the decrease from week 1 to week 6 was faster than the decrease from week 6 to week 12. It implied that the status of patients was getting well from week 1 to week 12.

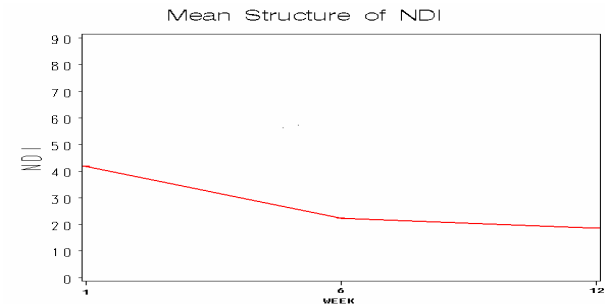


Figure 3.1: The average evolution of NDI over time

Exploring the Variance Structure

From Figure 3.2, it showed a non-constant variance function. It decreased from week 1 to week 12. Therefore, a complex variance structure would be a plausible starting point.

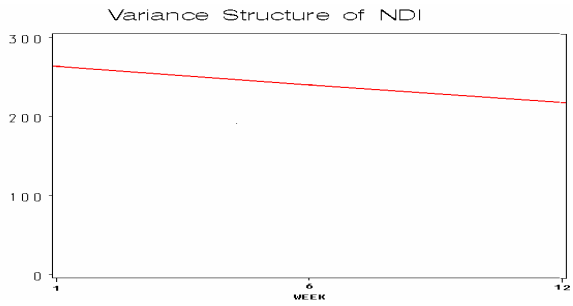


Figure 3.2: The variance structure of NDI over time

Exploring the Individual Profiles

The individual profile was displayed in Figure 3.3. It showed different trends of patients from week 1 to week 12.

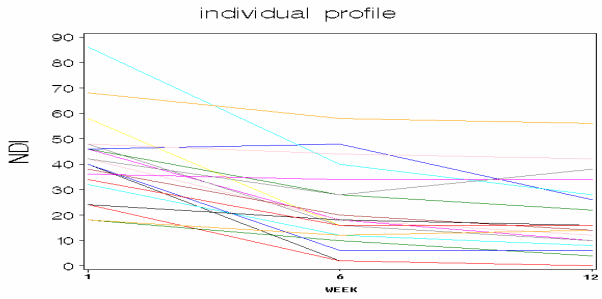


Figure3.3: The individual profile of NDI over time

Exploring the Correlation Coefficients

The correlation structure depended on a pair of time points described how the measurements within patient were correlated. One way displayed correlation structure was used by spearmen's correlation coefficients (Table 3.2). And another way was used by scatter plot (Figure 3.4). Both of them displayed very high correlation between measurements of the NDI at week 6 and week 12.

Table 3.2: The spearman correlation coefficients by NDI over time

	NDI at week 1	**NDI at week 6**	**NDI at week 12**
NDI at week 1	1.00000	0.60076	0.51135
NDI at week 6	0.60076	1.00000	0.90424
NDI at week 12	0.51135	0.90424	1.00000

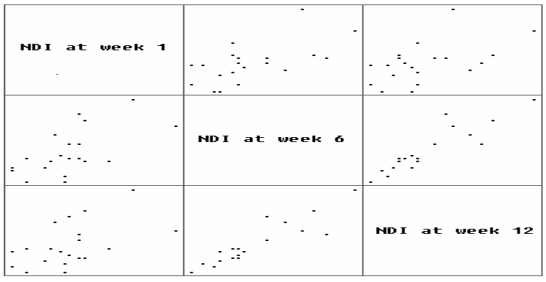


Figure 3.4: The scatter plot matrix by NDI over time

3.2 Descriptive statistics for the Binary NDIc

Howard Vernon developed the Neck Disability Index (NDI) in 1989. By the original report, it provided scoring intervals for interpretation, as follows:

$$NDI \quad \begin{cases} 0\text{-}10 = \text{no disability} \\ 10\text{-}30 = \text{mild} \\ 30\text{-}50 = \text{moderate} \\ 50\text{-}68 = \text{severe} \\ 68\text{-}100 = \text{complete} \end{cases}$$

It displayed the moderate was from 30 to 50 at the measurement of NDI. But in this special case, which only included NDI measurements of 20 patients from week 1 to week 12. Based on the requirements of the analysis, the secondary interest was categorized NDI into two level i.e. binary response. Therefore, according to the all measurements of patients, it would categorize NDI by mean (3.1). It meant that the NDI more than 27.533 would be indicated by '1', meant 'highly pain' and lower than 27.533 would be indicated by 0, meant 'less pain'.

$$response \;\; NDIc = \begin{cases} 1 & NDI \le 27.533 \\ 0 & otherwise \end{cases} \quad \text{.....(3.1)}$$

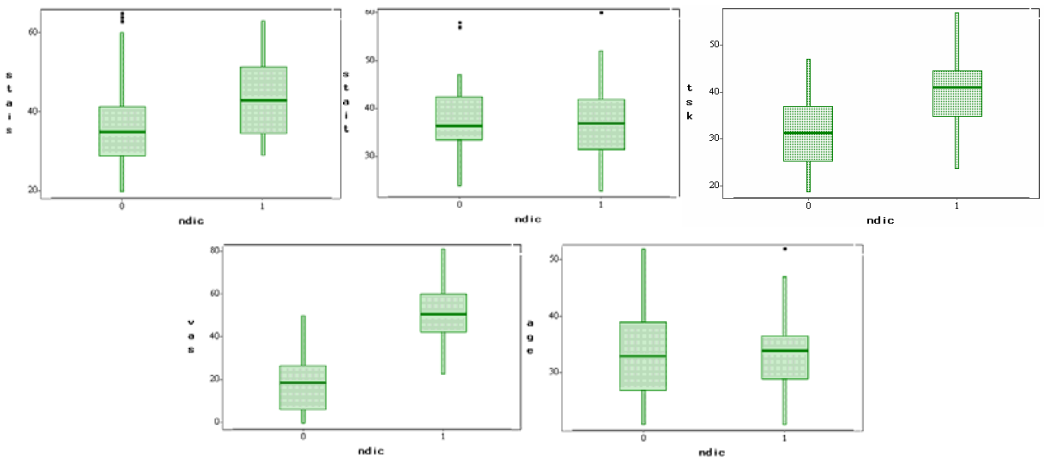


Figure 3.5: Box plots of NDIc with continues variables

The box plots of NDIc and continues covariates were shown in Figure 3.5. From these plots, STAIT and age plausibly looked like non-significant effects at the initial analysis. And covariates about STAIS, TSK, and VAS looked like probably significant effects.

Exploring the Average Evolution of the Proportion of 'Highly Pain'

The question of interest here was whether the percentage of 'highly pain' decreased over time as the result of the continues response before, and whether that evolution was different for gender as well as FA and SA. A summary of the number of patients in the analysis at each time point, and the number of patients with 'highly pain' ('1') was given in Table 3.3. A graphical representation was given in Figure 3.6.

Table 3.3: The descriptive of NDIc by categorized variables over time

	Week 1			**Week 6**			**Week 12**		
	N of '1'	**N**	**%**	**N of '1'**	**N**	**%**	**N of '1'**	**N**	**%**
NDIc	16	20	80%	7	20	35%	5	20	25%
By SEX									
SEX=1	8	12	66.67%	4	12	33.33%	3	12	25%
SEX=0	8	8	100%	3	8	37.50%	2	8	25%
By FA									
FA=1	12	13	92.31%	4	4	100%	1	1	100%
FA=2	2	4	50%	2	2	100%	2	3	66.67%
FA=3	2	3	66.67%	0	5	0%	2	4	50%
FA=4	0	0	.	1	9	11.11%	0	12	0%
By SA									
SA=1	6	6	100%	3	3	100%	0	0	.
SA=2	5	5	100%	2	2	100%	2	3	66.67%
SA=3	5	8	62.50%	1	4	25%	2	2	100%
SA=4	0	1	0%	1	11	9.09%	1	15	6.67%

From Table 3.3 and Figure 3.6, the results of the average proportion of 'highly pain' and the results by sex were very similar with the continues response of NDI before. The average proportion decreased from week 1 to week 12, and the decrease from week 1 to week 6 was faster than from week 6 to week 12. It primarily said when the NDI was categorized by mean the analysis might be feasible. But the average

proportions by FA and SA were not expected because of the limited dataset possibly.

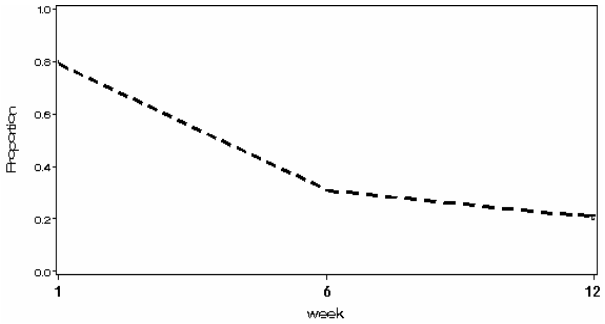


Figure 3.6: The proportion of 'Highly Pain'

Exploring the Correlation Coefficients

Based on a pair of time points and used Pearson's correlation coefficients, the correlation coefficients were shown in Table 3.4. It displayed high correlation of the measurement of the NDIc between week 6 and week 12.

Table 3.4: The Pearson correlation coefficients by NDIc over time

	NDIc at week 1	**NDIc at week 6**	**NDIc at week 12**
NDIc at week 1	1.00000	0.36690	0.28868
NDIc at week 6	0.36690	1.00000	0.78680
NDIc at week 12	0.28868	0.78680	1.00000

Chapter 4 Results of Statistical Analysis

4.1 Results for the Continues Response NDI

4.1.1 Fixed Effects

The primary interest of the analysis was to take five important covariates i.e. TSK, STAI-S, STAI-T, Gender and Age. There were several models assumed an unstructured type of variance structure and a simple correlation structure for the within-subject variability to be considered. First, saturated model included all the important covariates, linear time effects with covariates, as well as quadratic time effects with them and all the random intercepts, random linear time effects and random quadratic time effects. The Maximum Likelihood Estimate (MLE), standard errors and P-value for all fixed effects and all variance components in the saturated model were shown in Appendix Table A. The model was not to reparameterize the mean structure because it did not include the overall intercept, the overall slopes for the linear and quadratic time effects. Hence, in the saturated model here did not include the main effect of linear and quadratic time effects.

Reduction of mean structure was done via appropriate F-tests on various hypotheses of interest (2.2), where the same covariance structure and serial correlation structure were maintained. It was carried out by *contrast* statement step by step. Since the p-value of Chi-square distribution (P-value=0.6346) of all the deleted covariates together was not significant, it led to a model with a significant effect of TSK, a STAI-S, STAI-T, and significant different evolutions for gender over time. The detail steps of reduction were shown in Table 4.1.

Table 4.1: The results for reduction of mean structure

Deleted covariates	Chi-Square (P-value)	F (P-value)	Chi-Square (P-value)	F (P-value)
AGE **AGE*time** **AGE*time^2**	0.65 (0.8855)	0.22 (0.8842)	3.43 (0.6346)	0.69 (0.6398)
TSK *time^2	0.25 (0.6175)	0.25 (0.6218)		
STAIS*time^2	2.71 (0.0997)	2.71 (0.1131)		

Saturated model: *NDI=Age TSK STAIS STAIT SEX Age*time TSK*time STAIS*time STAIT*time SEX*time Age*time^2 TSK*time^2 STAIS*time^2 STAIT*time^2 SEX*time^2*

Final model*: NDI=TSK STAIS STAIT SEX TSK*time STAIS*time STAIT*time STAIT*time^2 SEX*time SEX*time^2*

4.1.2 Random Effects

Different from the fixed effects part, the random effects were done under the method of Restricted Maximum Likelihood Estimate (REML). Firstly, the simplified model with both random intercepts and random linear time effect was compared to the model with all random intercepts, random linear time effects and random quadratic time effects, where the mean structure of both models were obtained from the fixed effects part. The results of reduction of random effects were given in Table 4.2. The likelihood ratio test using the mixture Chi-square $\chi^2_{2:3}$ distributions led to a highly significant result (p=0.019). Similarly, the model only with random intercept or the multivariate regression model was compared with the model with all random intercepts, random linear time effects and random quadratic time effects separately (p=0.00275 and p<0.0001). Hence, all random intercepts, random linear time effects and random quadratic time effects should be retained.

Table 4.2: The result for reduction of random effects

Model	-2log REML	G^2	DF	P-value
Model with intercept,t&t^2	412.9			
Model with intercept, t	422.0	9.1	2:3	0.019
Model with intercept,t&t^2	412.9			
Model with intercept	426.1	13.2	1:3	0.00275
Model with intercept,t&t^2	412.9			
Multivariate model	444.1	31.2	3	<0.0001

And then, the covariance structure of the random effects would be checked under the method of Restricted Maximum Likelihood Estimate (REML). The comparison of unstructured and simple structure was given in Table 4.3. Through the likelihood ratio test used the chi-square distribution with degree freedom 5, it led to a significant result (p-value=0.0348). Hence, the 'Unstructured' of covariance structure should be accepted.

Table 4.3: The result for checking covariance structure

Covariance structure	-2log REML	G^2	DF	P-value
Unstructured	412.9			
Simple	424.9	12	5	0.0348

4.1.3 Serial Correlation

–2log likelihood (Restricted) was shown in Table 4.4. Because three of –2log likelihood (Restricted) gave the same results, it could not prove that there was a significant serial correlation. Therefore, the simple structure was adopted acquiescently.

Table 4.4: -2log REML value for various serial structures added to the model

Residual covariance structure	-2log REML
Simple	412.9
Gaussian	412.9
Exponential	412.9

4.1.4 Empirical Bayes Inference

Empirical Bayes (EB) estimates of the random intercepts, random slopes and random quadratic slopes were obtained. From the scatter plot of the random intercepts against the random slopes and the random quadratic slopes (Figure 4.1), the correlation between random intercepts and random slopes (ρ = -0.80893) was large as well as between random intercept and random quadratic slopes ($\rho = 0.75214$). It implied that a patient's self reported pain evolution very depended on his/her initial score.

Furthermore, The histograms of the random intercepts, random slopes and random quadratic slopes looked like asymmetry, this might be due to some patients with very different evolutions than the majority of patients.

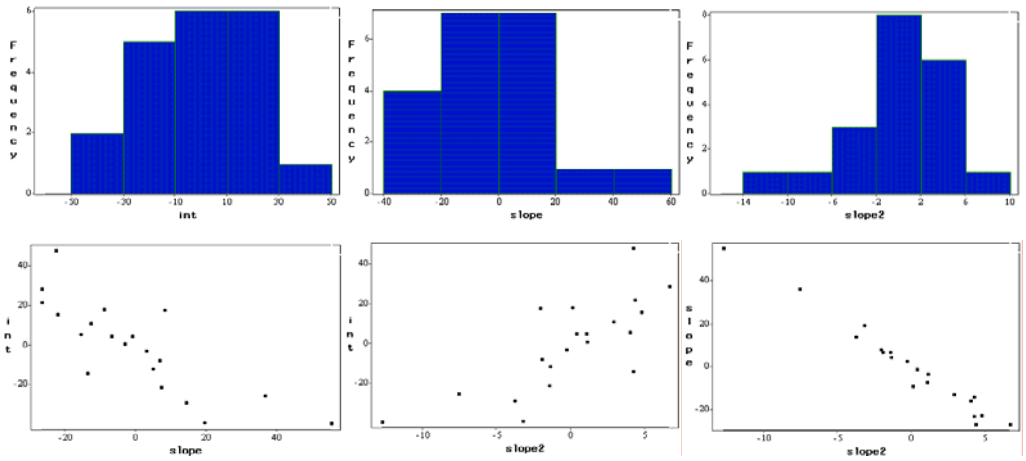


Figure 4.1: Histograms and scatter plots of the EB estimates for intercept, linear and quadratic time effects

4.1.5 Interpretation of the Final Model

Since the fixed effects, random effects and serial correlation were fitted, the results of fitting the final model under the restricted maximum likelihood estimation were shown in Table 4.5. The model included significant effects of TSK, STAI-S, STAI-T, as well as linear time effects with them and quadratic time effects with STAI-T. Also it indicated significant different evolutions for gender over time. The random intercepts represented most of the variability (d_{11}=574.35). The quadratic time effects (d_{33}=3.7320) represented less variability than the linear time effect (d_{22}=283.13). There are common within variability 18.6060.

For comparison the exploration phase with the confirmatory phase, the plot of average evolution and variance evolution for the observed value and the predicted value was displayed in Figure 4.2. On the one hand, the variance of predicted value was much smaller than the observed at each time point. On the other hand, the average evolutions of predicted and observed value were overlap. These indicated that even if the predicted average evolutions looked like better, but the deviation of variance

structures, the predicted value was far from the observed value in predicted individual values. Hence, the results of fitting model were farfetched.

Table 4.5: The estimates with the standard errors for all parameters of the final model

Effect	Parameter	Estimate (s.e)
TSK	β_2	-0.6556 (0.4362)
STAIS	β_3	0.5497 (0.2822)
STAIT	β_4	-2.3420 (0.9142)
Intercepts:		
Female	β_5	170.38 (47.6985)
Male	β_6	164.86 (49.7056)
TSK*time	β_8	0.3562 (0.1638)
STAIS*time effect	β_9	-0.2340 (0.1314)
STAIT*time effect	β_{10}	2.4416 (0.8429)
Time effect:		
Female	β_{11}	-148.11 (37.9370)
Male	β_{12}	-134.42 (39.6957)
STAIT* time^2 effect	β_{16}	-0.4801 (0.1890)
Time^2 effects:		
Female	β_{17}	28.6759 (7.5345)
Male	β_{18}	24.9032 (7.9037)
Covariance of b_i – subject:		
Var(b_{1i})-Patient	d_{11}	574.35
Var(b_{2i})-Patient	d_{22}	283.13
Var(b_{3i})-Patient	d_{33}	3.7320
Cov(b_{1i}, b_{2i})-Patient	$d_{12}=d_{21}$	-330.30
Cov(b_{1i}, b_{3i})-Patient	$d_{13}=d_{31}$	48.1790
Cov(b_{2i}, b_{3i})-Patient	$d_{23}=d_{32}$	-39.5310
Residual variance:		
Var(ε_{ij})	σ^2	18.6060
-2 Res Log Likelihood		412.9

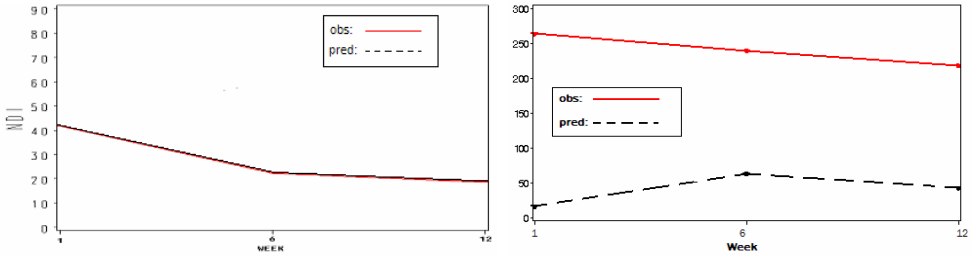


Figure 4.2: Average evolution, variance structure for predicted and observed value

4.1.6 Taking VAS, FA and SA into Account

The other interest of this analysis was to take the Visual Analog Scale (VAS) for pain, the status of physical and social activities and working status (FA and SA) into the model in order to explore the further analysis of NDI scores. The process of fitting the fixed effects, the random effects and the serial correlation were the same as before.

In the fixed effects, the saturated model included all covariates, time effects with covariates and quadratic time effects with covariates. Also via the appropriate F-tests on hypotheses of interest, a non-significant result of chi-squared distribution (P-value =0.7380) by *contrast* statement was obtained. Hence, the final model before checking the components and structure of covariance and serial correlation represented a significant effect of TSK, STAI-S, STAI-T, VAS, and significant different evolutions of physical and social activities, and significant different evolutions for gender over time. *(Final model included TSK, STAIS, STAIT, SEX, VAS, FA, SA, time effects with TSK, time effects with STAIS, time effects with STAIT, time effects with SEX, quadratic time effects with SEX, time effects with FA, quadratic time effects with FA)*

In the random effects, the comparison of model with different random components was shown in Table 4.6. When the model with both random intercepts and random linear time effects compared to the model with all random intercepts, random linear time effects and random quadratic time effects, The likelihood ratio test using the mixture $\chi^2_{2:3}$ distributions led to a non-significant result (p-value=0.1213). It meant the former is better than the latter. And then, the model with only random intercept or multivariate regression model was compared to the model with random intercepts and random linear time effects separately (p=0.0148 and p=0.0055). Hence, only random intercepts and random linear time effects should be retained.

Table 4.6: The result for reduction of random effect

Model	-2log REML	G^2	DF	P-value
Model with intercept,t&t^2	311.8			
Model with intercept, t	316.9	5.1	2:3	0.1213
Model with intercept, t	316.9			
Model with intercept	324.4	7.5	1:2	0.0148
Model with intercept, t	316.9			
Multivariate model	327.3	10.4	2	0.0055

In addition, through the process of the comparing unstructured (-2log REML=316.9) and simple structure (-2log REML=324.4), via the likelihood ratio test under the chi-square distribution with degree freedom 2, the 'Unstructured' of covariance structure was accepted (p-value=0.0235).

The selection of an appropriate residual covariance structure was shown in Table 4.7. Based on the -2log REML of the Gaussian serial correlation was smaller than two others, it might imply the residual covariance structure was 'Gaussian'.

Table 4.7: -2log REML value for various serial structures added to the model

Residual covariance structure	-2log REML
Simple	316.9
Gaussian	314.9
Exponential	316.9

Under the Gaussian serial correlation, fitting fixed effects, random effects must be carried out again. However, all components were the same as results above. Hence, EB and interpretation of the final model would be represented sequentially.

According to the Empirical Bayes (EB) estimates of the random intercepts and random slopes, the scatter plot and the histogram plots were shown in Figure 4.3. From scatter plot of the random intercepts vs. the random slopes, the correlation of them was large (ρ = -0.64601), implied that a patient's self reported pain evolution also depended on the initial score of patient after taking extra covariates (VAS, FA,

SA) into account. The histogram plots of random intercepts and random slopes did not look like normal, however, such histograms did not necessarily reflect the correct random effects distribution, and hence also that histograms of EB estimates might not be suitable for detecting deviations from the normality assumption.

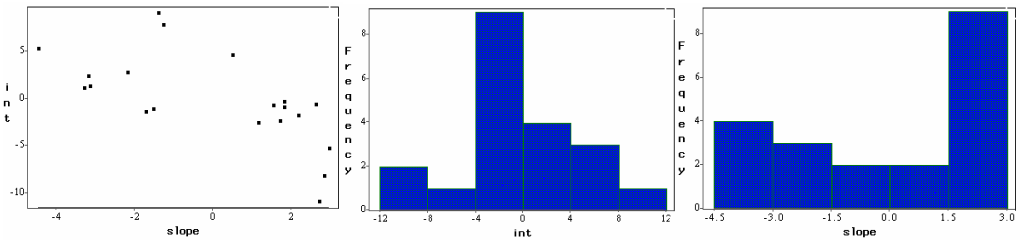


Figure 4.3: Histogram of the EB estimates for intercept, linear time effect and scatter plots for variance components

Finally, the result of the new final model was shown in Appendix Table B. The variability of random intercepts (d_{11}=78.2562) also represent more than the variability of random slopes (d_{22}=8.5067). The within-subject variability was 57.9011. Moreover, the VAS, FA and SA were also very important information to explore the NDI scores of patients over time. After that, the average evolution and variance evolution of the observed value and the predicted value were displayed in Figure 4.4. On the one hand, two average evolutions were also overlap. On the other hand, the variance of predicted was little smaller than the observed, and the trend of them might be superposition after 12 weeks. These results indicated that this final model was better and could be acceptable since considering more information (VAS, FA and SA) in the model.

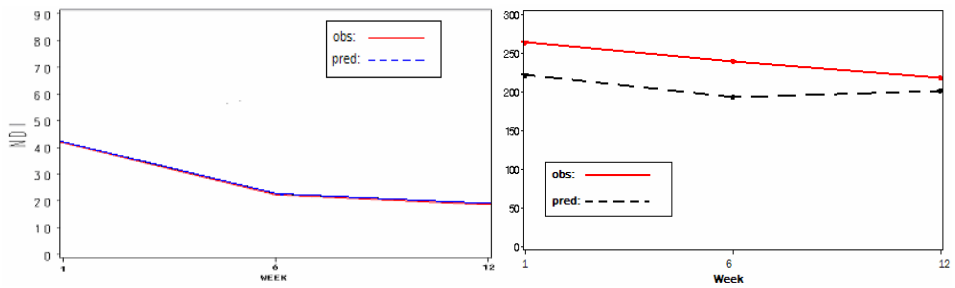


Figure 4.4: Average evolution, variance structure for predicted and observed value

4.2 Results of the Binary Response NDIc

4.2.1 Covariates Selection

Covariates selection was used univariate analysis under logistic regression. It depended on significant at the level 0.25 as Hosmer and Lemeshow recommended (Agresti 2002). The details of each covariate under univariate analysis were displayed in Table 4.8.

Table 4.8: Results of univariate analysis under logistic regression

Likelihood ratio test		**Likelihood ratio test**	
Variables	**P-value**	**Variables**	**P-value**
TSK	<.0001	VAS	<.0001
STAIT	0.8875	SEX	0.3415
STAIS	0.0179	FA	<.0001
AGE	0.8734	SA	<.0001

Consequently, the p-values of variables TSK, STAIS, VAS, FA and SA were less than 0.25 and would be considered in further analysis.

4.2.2 Marginal Models

As analysis of the continues response NDI, firstly, only covariates of TSK, STAI-S, STAI-T, gender and age were considered. From Table 4.8, the model only included TSK and STAI-S. Two methods –GEE, Alternative Logistic Regression (ALR) were used to obtain marginal models for the binary response NDIc. Based on the covariates selection, the saturated model included TSK, STAIS, the linear time effect, the quadratic time effect, and time and quadratic time effect with TSK and STAIS.

Generalized Estimating Equations (GEE)

Firstly, the model selection must be carried out. Under unstructured working correlation assumption, via appropriate F-tests used *contrast* statement step by step

(Table 4.9), the initial model before checked the working correlation assumption was obtained. It only included the covariates TSK and time effects.

Table 4.9:Results of deleted covariates step by step via appropriate F-tests used contrast statement in SAS

Deleted covariates	DF	Chi-Square (P-value)
STAIS **STAIS*time** **STAIS*time^2**	3	0.74 (0.8640)
TSK *time^2	1	2.55 (0.1102)
Time^2	1	2.49 (0.1142)
TSK*time	1	0.04 (0.8338)

Thereafter, fitting a GEE model with an independence, exchangeable and unstructured working correlation assumption were carried out. A summary of the final results for each working correlation assumptions was given in Table 4.10.

Table 4.10: Results of GEE under working correlation assumptions

GEE (Unstructured)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-1.6117	1.7281	1.3293	0.3510	0.2253
TSK	0.0861	0.0406	0.0359	0.0341	0.0164
Time	-0.8207	0.2992	0.2865	0.0061	0.0042
GEE (Exchangeable)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-1.5393	1.8932	1.5283	0.4162	0.3138
TSK	0.0959	0.0431	0.0414	0.0261	0.0204
Time	-1.0286	0.3299	0.3372	0.0018	0.0023
GEE (Independence)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-2.7772	1.9426	1.5615	0.1528	0.0753
TSK	0.1254	0.0443	0.0381	0.0046	0.0010
Time	-0.9514	0.4184	0.3887	0.0230	0.0144

Apparently, the exchangeable working assumption gave the smallest difference of model based and empirical standard error, in other words, exchangeable working correlation assumption closed to the truth in GEE model. But, in general, the unstructured working correlation assumption had a greater practicality rather than exchangeable working correlation assumption. Hence, although exchangeable correlation assumption closed to the truth, the unstructured correlation assumption was preferred in GEE model.

Therefore, under unstructured working correlation assumption, the time effect was highly significant, which indicated that the probability of 'highly pain' (NDIc=1) was strongly related to the time elapsed after checking TSK score. In addition, the parameter estimate of TSK indicated a positive relationship with the probability of 'highly pain'.

Alternating Logistic Regression (ALR)

Under the SAS *genmod* procedure used the option *logor=fullclust/exch* in the repeated statement, the ALR could not be carry out because problems in log odds ratio regression computation and in parameter estimate covariance computation. Thus, due to the computational problems of SAS software, fitted ALR was terminated.

4.2.3 Random Effects Model

Compared with marginal models, which described the average response conditional on only the covariates, random effects model described the average response conditional on the covariates and the random effects.

The Generalized Linear Mixed Model (GLMM)

Two possibilities, on the one hand, since patient-subjects could possibly vary, not only in the levels of their probabilities of 'highly pain', but also in the rates at which these probabilities change, both random intercepts and slopes were considered. On the other

hand, the variation was only due to the levels of probabilities of 'highly pain', only random intercept was considered. The results of both were shown in Table 4.11. These results were obtained from a model which contained covariates of interest and parameter estimates from GEE model.

Table 4.11: Parameter estimates and standard error for GLMM

***GLMM** (only random intercepts)*					
Fixed Parameters			**Covariance Parameters**		
Parameter	**Estimate**	**Std. Error**	**Parameter**	**Estimate**	**Std. Error**
Intercept	-5.3201	6.0025	**d**	4.4879	2.1850
TSK	0.3053	0.1695			
Time	-3.0147	1.5163			
-2 Log Likelihood			**49.9**		
***GLMM** (both random intercepts and random slopes)*					
Fixed Parameters			**Covariance Parameters**		
Parameter	**Estimate**	**Std. Error**	**Parameter**	**Estimate**	**Std. Error**
Intercept	-6.6811	13.7653	$\mathbf{d_{11}}$	37.1958	90.8814
TSK	0.4574	0.4259	$\mathbf{d_{12}}$	3.0221	30.5781
Time	-5.5758	3.9223	$\mathbf{d_{22}}$	4.9656	16.5252
-2 Log Likelihood			**48.7**		

Comparing two GLMMs via mixture chi-square $\chi^2_{1:2}$ distributions, it led to a non-significant result (p-value=0.4110). This implied that only the random intercept was important to reflect between subject variability. Furthermore, in GLMM, the results also indicated that the probability of 'highly pain' strongly related to the time elapsed as well as TSK. Finally, an approximate measure of intra cluster-correlation was calculated. Based on both the random intercepts variance (d=4.4879) and the variance of the standard logistic density ($\pi^2/3$), as follows: $\rho = d / \pi^2 / 3 + d = 0.5773$.

Comparing results between GEE and GLMM, formulations could be presented as follows:

$$Logit(\hat{\pi}_{ij})_{GEE} = -1.6117 + 0.0861 * TSK - 0.8207 * \text{time}_{ij} \quad \text{.....(4.1)}$$

$$Logit(\hat{\pi}_{ij} \mid b_i)_{GLMM} = -5.3201 + 0.3053 * TSK - 3.0147\,4 * \text{time}_{ij} + b_i \quad \text{.....(4.2)}$$

π_{ij} denoted the probability of 'highly pain' in NDIc for the i^{th} subject at the j^{th} time point. In the second set of expressions, b_i was the random intercepts of the i^{th} subject.

These formulations clearly explained that the probabilities of 'highly pain' in the marginal model (GEE) were 'population averages', depended only on TSK and time, whereas the random effects model (GLMM) depended not only on TSK and time, but also on the random effects.

4.2.4 Empirical Bayes Inference

The histogram of the EB estimates of random intercepts was shown in Figure 4.5. It represented random intercepts did not look like normality.

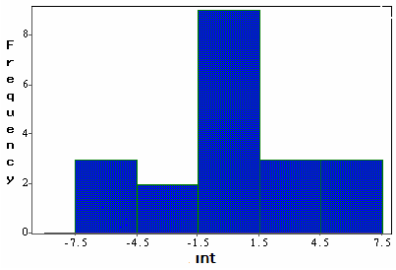


Figure 4.5: Histogram of the EB estimates of random intercepts

4.2.5 Taking VAS, FA and SA into Account

When taking VAS, FA and SA into account, surprisingly, there was only a significant VAS effect in GEE before checking working correlation assumption. Therefore, The results of fitting a GEE model with an independence, exchangeable and unstructured working correlation assumptions were display in Table 4.12.

Through the comparison of standard errors between empirical and model-based, the unstructured working correlation assumption gave a smallest difference. Hence, unstructured correlation was closed to the true in GEE model.

Table 4.12: Results of GEE under working correlation assumptions

GEE (Unstructured)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-4.7490	1.2204	1.1327	<.0001	<.0001
VAS	0.1351	0.0330	0.0298	<.0001	<.0001
GEE (Exchangeable)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-4.9449	1.3343	1.2024	<.0001	0.0002
VAS	0.1433	0.0357	0.0338	<.0001	<.0001
GEE (Independence)					
Parameter	**Estimate**	**Std. Errors**		**P-value**	
		Model-Based	**Empirically Corrected**	**Model-Based**	**Empirically Corrected**
Intercept	-4.9760	1.2847	1.2280	<.0001	0.0001
VAS	0.1403	0.0340	0.0303	<.0001	<.0001

Similarly in Section 4.2.3, random effects model with the random intercepts and slopes compared with the model only the random intercepts. The results of two models were shown in Table 4.13.

Table 4.13: Parameter estimates and standard error for GLMM

***GLMM** (only random intercepts)*					
Fixed Parameters			**Covariance Parameters**		
Parameter	**Estimate**	**Std. Error**	**Parameter**	**Estimate**	**Std. Error**
Intercept	-8.6585	3.4845	**d**	2.4054	1.2680
VAS	0.2483	0.09908			
-2 Log Likelihood			**32.9**		
***GLMM** (both random intercepts and random slopes)*					
Fixed Parameters			**Covariance Parameters**		
Parameter	**Estimate**	**Std. Error**	**Parameter**	**Estimate**	**Std. Error**
Intercept	-8.9082	3.8599	$\mathbf{d_{11}}$	6.9325	12.1577
VAS	0.2555	0.1101	$\mathbf{d_{12}}$	-0.2990	2.5542
			$\mathbf{d_{22}}$	0.1467	0.7793
-2 Log Likelihood			**32.8**		

According to mixture chi-square $\chi^2_{1:2}$ distributions, it led to a non-significant result (p-value=0.8515). This implied that only the random intercept was important in reflecting between-subject variability. Furthermore, the probability of 'highly pain' strongly related to the score of VAS after took VAS, FA, and SA into account.

The approximate measure of intra cluster-correlation was calculated to $\rho = 0.4226$. Moreover, comparing formulations between GEE and GLMM as follows:

$$Logit(\hat{\pi}_{ij})_{GEE} = -4.7490 + 0.1351 * VAS \quad \text{……..…….....……..(4.3)}$$

$$Logit(\hat{\pi}_{ij} \mid b_i)_{GLMM} = -8.6585 + 0.2483 * VAS + b_i \quad \text{…….....…(4.4)}$$

Finally, The histogram of the EB estimates of random intercepts was shown in Figure 4.6, which also did not look like normality.

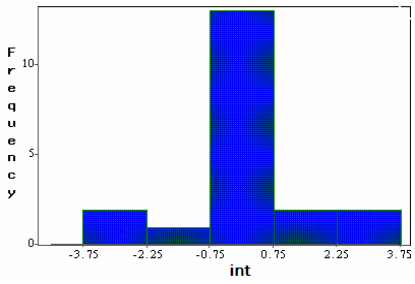


Figure 4.6: Histogram of the EB estimates of random intercepts

Chapter 5 Discussion and Conclusion

5.1 Discussion

From the WHIPLASH dataset, the main objective was to investigate the prospective longitudinal development of NDI scores by some psychological changes and the basic information of patients after a whiplash trauma. In addition, the analysis which was interested in whether or not it was possible to categorize the NDI into two levels by mean instead of the complex categorization as Howard Vernon done in 1989 (Section 3.2).

Depends on the continue response NDI, fitting the linear mixed model explicitly in two models with different covariates components. The results of these two models obtained different mean structures.

(PART 1) Firstly, only considered covariates of TSK, STAIS, STAIT, Age and Gender, the mean structure included significant effects of TSK, STAI-S, STAI-T, as well as linear time effect with them, also a significant different evolutions for gender over time. And then in the random effects, through the likelihood ratio test, all the random intercepts, the random linear time effects and the random quadratic time effects should be retained. And unstructured covariance structure was confirmed. Finally, under the three residual covariance structures, the same results of –2log-likelihood (Restricted) was obtained, so that the simple covariance structure was adopted. Based on the final model, the variances and average evolutions of the predicted and the observed value were compared (Figure 4.2). Although a great overlap in average evolutions, it might be due to the small sample size. However, comparison of two variances evolutions was very deviation, which implied that the result of ***PART 1*** was not prefect and need an improvement.

(PART 2) Hence, secondly, took more information (VAS, FA and SA) into account, the mean structure further identified that all of them jointed in the model with important roles. It implied that the information from new actors could also reflect the response of NDI scores. In the random effect part, there were only the random intercepts and the random linear time effects. In addition, unstructured covariance structure and the Gaussian residual covariance structure were obtained. And then the comparison of the variances and average evolutions of the predicted and the observed value, not only the average evolutions were overlap, but also the variance of predicted was little smaller than the observed, and the trend of them might be superposition after 12 weeks. Hence, the second final model was accepted and it could fully interpret or reflect the continue response NDI.

On the other hand, the physicians were very interested in splitting the group of patients in two groups. In this analysis, the NDI value was categorized into two levels by mean (NDIc). The objective was to investigate whether it is possible to simplify and replace the continue response NDI.

(PART 3) By the binary response NDIc, firstly, also only consider covariates of TSK, STAIS, STAIT, Age and Gender. In GEE, under the unstructured working correlation assumption it indicated a significant and positive relationship with the probability of ‘highly pain’ on TSK, also a highly significant on time indicated that the probability of ‘highly pain’ was strongly related to the time elapsed after checked TSK score. However, due to the computational problems of SAS software, fitted ALR was not possible to carry out. In GLMM, the results also indicated that the probability of ‘highly pain’ strongly related to the time elapsed and the score of TSK the similar as GEE. Furthermore, it displayed that only the random intercept was important to reflect between-subjects variability.

(PART 4) Secondly, took VAS, FA, SA into account, the different GEE model was

obtained and only VAS was significant. In GLMM, the model included significant effects of VAS and random intercepts.

In Table 5.1, comparison of not only ***PART 1*** and ***PART 3***, but also ***PART 2*** and ***PART4***, the great difference was discovered. It implied that the model was no longer stable and sufficient after the response NDI categorized into two levels by mean. It caused that the model loss more information and did not reflect the NDI scores adequately so far.

Table 5.1: Psychological and basic information reflected the NDI in different PARTs

PART 1 (Continues)	**PART 3 (Binary)**	**PART 2 (Continues)**	**PART 4 (Binary)**
☑TSK	☑TSK	☑TSK	☐TSK
☑STAIS	☐STAIS	☑STAIS	☐STAIS
☑STAIT	☐STAIT	☑STAIT	☐STAIT
☑SEX	☐SEX	☑SEX	☐SEX
☐AGE	☐AGE	☐AGE	☐AGE
		☑FA	☐FA
		☑SA	☐SA
		☑VAS	☑VAS

5.2 Conclusion

On the one hand, not only the various psychological factors such as TSK, STAIS, STAIT, but also VAS and the physical and social activities and working status could reflect the longitudinal development of NDI value. On the other hand, when the response was categorized into two levels by mean, the results could not correctly reflect the NDI value i.e. the binary NDIc could not replace the NDI scores. Furthermore, the further analysis will be carried out when the dataset was extended and recorded the information at more time points.

Appendix

Appendix Table A

Effect	Parameter	Estimate (s.e)	P-value
AGE effect	β_1	-0.4089 (0.8771)	0.6460
TSK	β_2	-1.2706 (1.0593)	0.2435
STAIS	β_3	1.6276 (0.7281)	0.0359
STAIT	β_4	-3.2556 (1.0415)	0.0046
Intercepts:			
Female	β_5	201.24 (55.5913)	0.0018
Male	β_6	189.83 (53.1977)	0.0020
AGE*time effect	β_7	0.1315 (0.8386)	0.8769
TSK*time effect	β_8	0.8481 (0.9603)	0.3859
STAI-S*time effect	β_9	-1.3055 (0.6968)	0.0731
STAI-T*time effect	β_{10}	3.3837 (0.9938)	0.0021
Time effect:			
Female	β_{11}	-164.61 (48.1380)	0.0026
Male	β_{12}	-148.11 (45.2239)	0.0037
AGE*time^2 effect	β_{13}	-0.00688 (0.1796)	0.9698
TSK*time^2 effect	β_{14}	-0.08675 (0.2075)	0.6795
STAI-S*time^2 effect	β_{15}	0.2315 (0.1468)	0.1283
STAI-T*time^2 effect	β_{16}	-0.7011 (0.2171)	0.0034
Time^2 effects:			
Female	β_{17}	31.3792 (9.9111)	0.0046
Male	β_{18}	27.3053 (9.2231)	0.0075
Covariance of b_i – subject:			
Var(b_{1i})-Patient	d_{11}	570.81	
Var(b_{2i})-Patient	d_{22}	473.88	
Var(b_{3i})-Patient	d_{33}	19.1777	
Cov(b_{1i}, b_{2i})-Patient	$d_{12}=d_{21}$	-427.95	
Cov(b_{1i}, b_{3i})-Patient	$d_{13}=d_{31}$	79.9407	
Cov(b_{2i}, b_{3i})-Patient	$d_{23}=d_{32}$	-94.4209	
Residual variance:			
Var(ε_{ij})	σ^2	4.2595	
-2Log-likelihood		415.1	

Appendix Table B

Effect	Parameter	Estimate (s.e)
TSK	β_2	0.2730 (0.3809)
STAIS	β_3	0.7197 (0.2512)
STAIT	β_4	-1.3096 (0.3716)
VAS	β_5	0.3179 (0.08025)
Intercepts: Female	β_6	65.4569 (26.4475)
Male	β_7	38.8106 (27.1057)
FA1	β_8	43.1029 (23.6103)
FA2	β_9	-3.8037 (27.9001)
FA3	β_{10}	19.4296 (24.4758)
FA4	β_{11}	38.8106 (27.1057)
SA1	β_{12}	66.5338 (27.9263)
SA2	β_{13}	45.2227 (27.4237)
SA3	β_{14}	51.4365 (27.2002)
SA4	β_{15}	38.8106 (27.1057)
TSK*time effect	β_{17}	-0.06873 (0.1644)
STAI-S*time effect	β_{18}	-0.2482 (0.1228)
STAI-T*time effect	β_{19}	0.4568 (0.1779)
Time effect: Female	β_{21}	-45.6638 (17.7271)
Male	β_{22}	-17.7109 (17.6705)
FA1	β_{23}	-39.5415 (15.3133)
FA2	β_{24}	18.1211 (22.3161)
FA3	β_{25}	-10.3429 (15.9199)
FA4	β_{26}	-9.4250 (7.1891)
Time^2 effects: Female	β_{36}	8.3375 (3.2838)
Male	β_{37}	1.6572 (3.0074)
FA1	β_{38}	9.4776 (3.4082)
FA2	β_{39}	-3.8445 (4.9026)
FA3	β_{40}	1.6572 (3.0074)
FA4	β_{41}	-1.8850 (1.4378)
Covariance of b_i – subject:		
Var(b_{1i})-Patient	d_{11}	78.2562
Var(b_{2i})-Patient	d_{22}	8.5067
Cov(b_{1i}, b_{2i})-Patient	$d_{12}=d_{21}$	-31.1842
Measurement error variance:		
Var($\varepsilon_{(1)ij}$)	σ^2	1.1038
Gaussian serial correlation: Var($\varepsilon_{(2)ij}$)	τ^2	57.9011
Rate of exponential decrease	$1/\phi$	1.5907
-2 Res Log Likelihood		318.2

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