KU LEUVEN

FACULTY OF SCIENCE

Exam Assignment

Concepts of multilevel, longitudinal, and mixed models

Laura Juliana GUERRERO VELASQUEZ
laurajuliana.guerrerovelasquez@student.kuleuven.be
Daniel Gerardo GIL SANCHEZ
daniel.gilsanchez@student.kuleuven.be

Prof. Geert Verbeke

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Exam Assignment

The post-operative evolution of cognitive status in elderly patients that suffered from hip-fracture is of interest in comparison with their pre-operative status. For this reason, a longitudinal observational study was performed on 59 patients where different variables were collected. Before the surgery, the patients were classified as neuro-psychiatric or not neuro-psychiatric according to their status; also, their *age* and their *housing* situation were collected to be able to control the results by these two factors. After the surgery, their physical activity was measured several times using the Mini Mental State Examination (*MMSE*), a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment (Pangman et al., 2000). These measures were taken in all patients at days 1, 3, 5, 8 and 12 after the surgery.

The goal of this study is to compare the evolution of MMSE in both groups, neuro-psychiatric and not neuro-psychiatric, and to evaluate the effects of housing and age on these evolutions. In the following, a descriptive analysis is performed to identify patterns in the data. Then, different linear mixed models are conducted to compare these groups. Finally, a dichotomization of the *MMSE* measure is considered and a logistic mixed model is performed.

A description of the data, differentiating between neuro-psychiatric and not neuro-psychiatric, is given in Table 1. The number of patients in the not neuro-psychiatric group is 40 and 19 in the neuro-psychiatric group. The age in the first group varies between 65 and 95 years, whereas in the second group the range is between 68 and 94 years. The distribution of the housing situation in both groups is completely different: in the not neuro-psychiatric group the majority lives with their family or partner, while in the neuro-psychiatric group the majority lives in a nursing home[1]. In regard to the MMSE, there is a clear difference in the mean of both groups, the first group has an

	Not Neuro-Psychiatric	**Neuro-Psychiatric**
Number of patients	40	19
Age		
Mean	78.18	79.89
Std	8.86	6.57
Range	$65 - 95$	$68 - 94$
Housing (%)		
Alone	36.14	24.32
With family	51.2	20.27
Nursing home	12.65	55.41
MMSE		
Mean	21.58	12.89
Std	6.75	8.53
Range	$4 - 30$	$0 - 26$

Table 1: Descriptive statistics

[1]Note that five patients do not have information in their housing situation. Three of them belong to the not neuro-psychiatric group and the remaining to the other group.

average score of 21.58 while the second has a lower average of 12.89.

Due to unknown reasons, 20 (36%) out of the 59 patients left the study prematurely. Table 2 summarizes the number of patients still in the study at each occasion, for both groups separately. Note that on the first day, one patient of the neuro-psychiatric group does not have a measure.

In this study, it is assumed that there is not a relationship between leaving the study prematurely and the outcome, MMSE. Mainly, because the reason for leaving the study early may be related to a good recovery process after the surgery.

	# Observations		
Time (days)	**Not Neuro-Psychiatric**	**Neuro-Psychiatric**	**Total**
1	40	18	58
3	38	19	57
5	40	19	59
8	36	16	52
12	27	11	38

Table 2: Number of observations taken at each occasion, for each group and in total

Now, given the purpose of performing a mixed model, three aspects of the data are analyzed in detail: the mean structure, the variance structure and the correlation structure. According to Verbeke and Molenberghs (2000), the results of the exploration for the average evolution are useful in order to choose a fixed-effects structure of the linear mixed model. Likewise, the results of the exploration for the variance evolution and correlation structure are useful in the selection of an appropriate random-effects structure.

The individual profiles are displayed in Figure 1, the mean profiles per group are shown in Figure 2 and the group difference is plotted in Figure 3. The individual profiles indicate that between subjects, the MMSE varies a lot within each group, and this variation seems to be constant over time. Additionally, there are some patients with very low scores in the not neuro-psychiatric group as well as some patients with very high scores in the neuro-psychiatric group.

In general, patients with lower (higher) score tend to be the lowest (highest) over time, which is a clear indication of high correlation within patients. It is also evident the lack of information in the later study times, mainly at day 12, suggesting that trends at later times should be treated with caution.

The average profiles show a defined difference between both groups over time, where the not neuro-psychiatric a has greater mean score than its counterpart. Also, the overall trend in each group seems not to fluctuate drastically over time. The not neuro-psychiatric group average starts around 21 and increases a little bit, whereas the average of the neuro-psychiatric starts at approximately 13, increases in the next

measure but then drops on day 8 to finally increase at the end of the study. This plot is of primary interest because it indicates that the evolution is almost flat when considering the complete scale of the MMSE (from zero to 30).

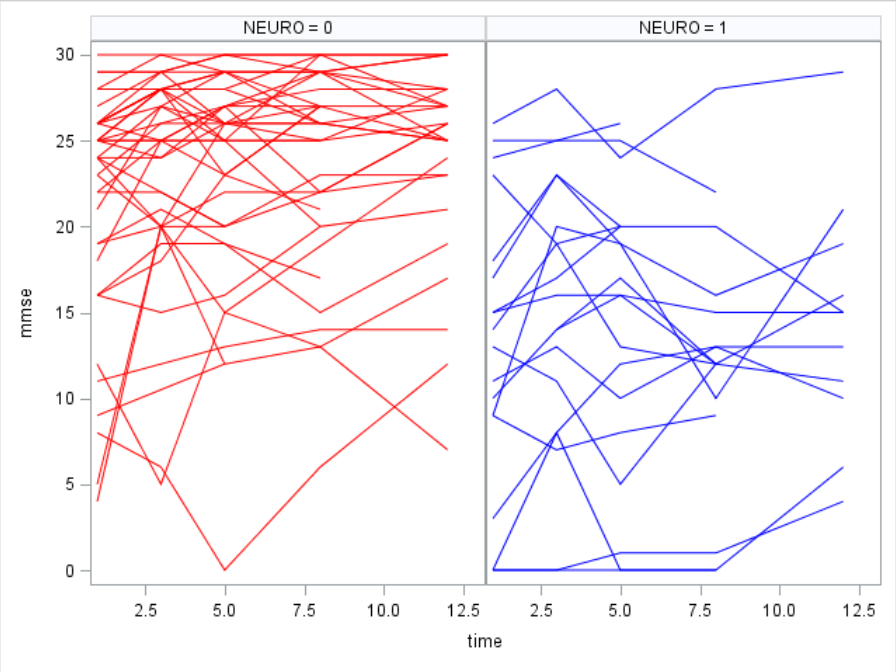


Figure 1: Individual profiles for not neuro-psychiatric (Left) and neuro-psychiatric patients (Right)

In particular, the difference is almost constant on days 1, 3 and 5. The largest difference is observed on the eighth day, but then decreases again on day 12. Of course, at this point it is not yet possible to decide whether the difference between groups is significant or not.

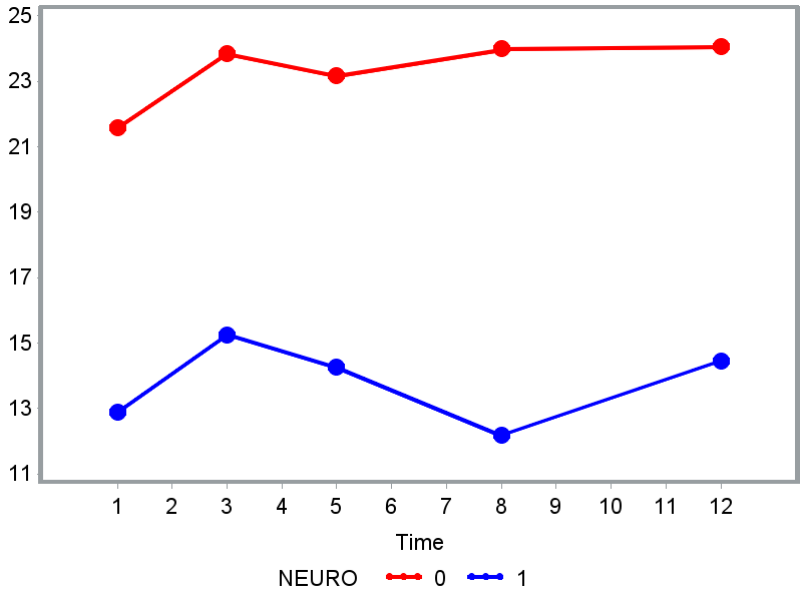


Figure 2: Average evolution

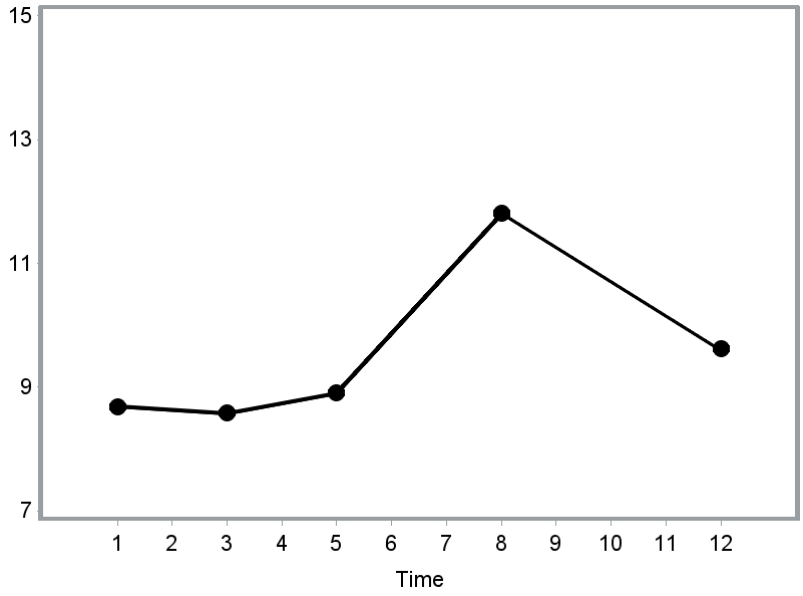


Figure 3: Group average difference

In the perspective of the variance structure, Figure 4 shows the variance function for each group. Both groups have a decreasing trend over time; this could be explained by the number of patients that left the study before it finished. The group of not neuropsychiatric patients present less variability in all measures and both variance functions seem to be parallel.

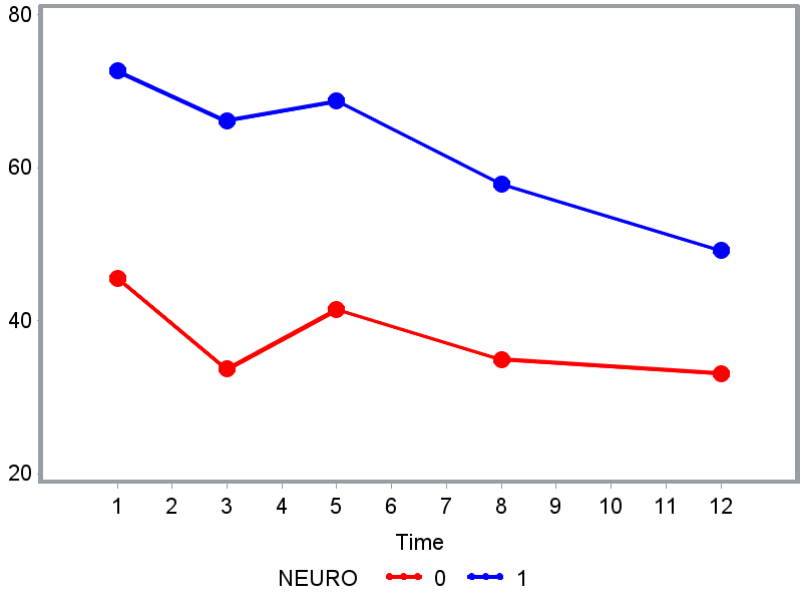


Figure 4: Variance function

Concerning the correlation structure, Figure 5 and Table 3 shows the correlation coefficient between each pair of time measurement. Although there are some differences in these coefficients, the correlation over time stays relatively constant. As for the values, all correlations are highly positive which means the evolution of a patient depends highly on how its previous scores were.

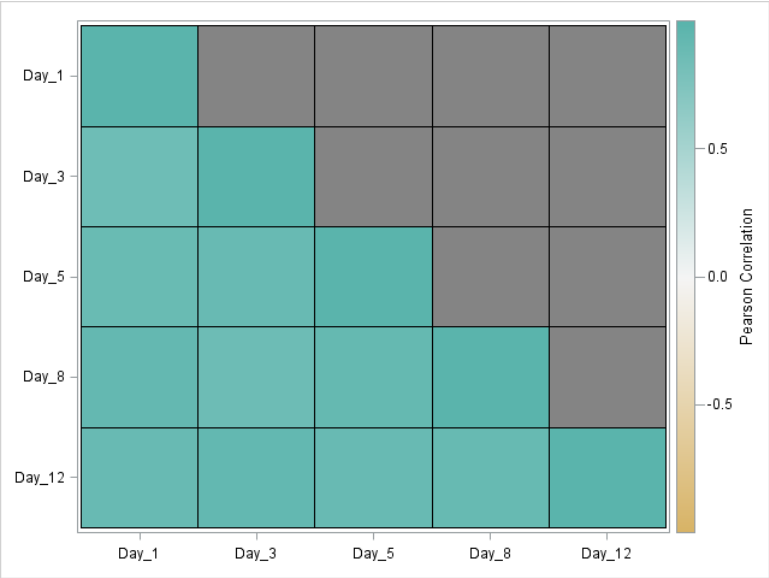


Figure 5: Correlation Matrix. HeatMap

	Day 1	Day 3	Day 5	Day 8	Day 12
Day 1	1	0.874	0.905	0.939	0.910
Day 3	0.874	1	0.910	0.880	0.944
Day 5	0.905	0.910	1	0.935	0.912
Day 8	0.939	0.880	0.935	1	0.920
Day 12	0.910	0.944	0.912	0.920	1

Table 3: Correlation between time measurements

To sum up, the descriptive part gives some insights on how the model should be defined. First, there are group differences in the average MMSE, where the group of patients that were classified as not neuro-psychiatric presents higher scores over time. So, in order to be able to determine whether this difference is significant, the group is considered in the model as a fixed effect. As a consequence, the fact of belonging to each group defines a different fixed intercept.

The evolution of the patients is of primary interest, so Time is also included in the fixed part. Despite the fact group profile evolutions seem parallel over time, an interaction between group-time is considered to allow different slopes for the groups.

In respect to the linearity of the relationship between the response variable and the covariates, a logarithmic transformation of time is used to improve this condition.

Finally, having repeated measurements of the patients make essential to consider the within-patient correlation model by random effects. The individual profiles showed there is a great amount of variability that can be explained by subject specific intercepts in the model. Additionally, the variance structure leads to conclude that the variability is not constant over time, so random slopes is also considered in the model.

Therefore, a linear mixed model is considered to study the MMSE evolution, assuming that, on a logarithmic timescale, this evolution is linear over time for both groups.

The model is given by:

$$Y_{ij} = \begin{cases} (\beta_{10} + b_{0i}) + (\beta_{11} + b_{1i}) ln(time_{ij}) + \epsilon_{ij} & \text{if Not neuro-psychiatric} \\ (\beta_{20} + b_{0i}) + (\beta_{21} + b_{1i}) ln(time_{ij}) + \epsilon_{ij} & \text{if Neuro-psychiatric} \end{cases} \quad (1)$$

Where Y_{ij} is the response variable, MMSE score, for patient *i* in time *j*. The average intercepts are represented by β_{10} and β_{20} and the slopes β_{11} and β_{21} for not neuro-psychiatric and neuro-psychiatric patients, respectively.

Moreover, each patient has its own intercept and slope, described by the random effects b_{0i} and b_{1i} which are assumed to follow a two-dimensional normal distribution with mean zero and covariance matrix **D**. At the same time, these random-effects are independent of the error terms ϵ_{ij}, which are also assumed to follow a normal distribution with mean zero and variance σ^2.

It is important to notice that even though the interaction is not explicitly showed in model (1), it is still there. As explained before, the purpose of the interaction is to allow each group to have its own slope, as it happens here with β_{11} and β_{21}. Similarly, the variable group is not in the model explicitly, although it is reflected by having a different intercept for each group (β_{10} and β_{20}).

In this context, the first step is to fit model (1) in a statistical software. In this study, SAS is used because it allows to fit different models in an easy way, specifically the procedure $\mathrm{proc\ mixed}$. As a result, the interaction turns out to be not significant to explain the evolution of MMSE ($F = 0.62$, $p - value = 0.4319$). This means that the groups do not have different slopes over the time, implying a parallel behavior (as seen also in Figure 2).

Therefore, the fixed part of the model is modified by removing the interaction term. Hence, model (1) can be rewritten as model (2):

$$Y_{ij} = \begin{cases} (\beta_{10} + b_{0i}) + (\beta_{1} + b_{1i}) ln(time_{ij}) + \epsilon_{ij} & \text{if Not neuro-psychiatric} \\ (\beta_{20} + b_{0i}) + (\beta_{1} + b_{1i}) ln(time_{ij}) + \epsilon_{ij} & \text{if Neuro-psychiatric} \end{cases} \quad (2)$$

Table 4 shows the estimations for each parameter. Note that instead of showing an estimation for each patient, it is shown the estimates of the fixed-effects, using the neuro-psychiatric group as reference, as well as the variance components of the random-effects.

The variability of the random intercepts is 47.22 while the variability of the random slopes is just 0.17, suggesting there is a lot of variability in the patients' deviations from the grand intercept but not much in the deviations in slopes from the estimated fixed slope for time. The covariance between these random-effects is -2.26, implying that there is a negative correlation between them. And the variance of the error component is 5.97.

Regarding the fixed-effects, the average MMSE across all patients from the neuro-psychiatric group at the start of the treatment is 12.87, whereas the average MMSE from the not neuro-psychiatric group is $12.87 + 9.12 = 21.99$. The effect of time suggests that the cognitive condition improves over time, where an increase of one unit in the

	Estimate	Std. Error
Fixed-effects		
Intercept	12.87	1.53
Ln(Time)	0.86	0.19
Not Neuro	9.12	1.78
Random-effects		
Var(Intercepts)	47.22	
Var(Slopes)	0.17	
Cov(Int,Slopes)	-2.26	
Var(Error)	5.97	

Table 4: Parameter estimations of model (2)

logarithmic timescale lead to an average increase of 0.86 units in the MMSE score, independent of the group a patient belongs to. So, the average evolution of MMSE for both groups is given by:

$$E(Y_{ij}) = \begin{cases} 21.99 + 0.85t & \text{if Not neuro-psychiatric} \\ 12.73 + 0.85t & \text{if Neuro-psychiatric} \end{cases}$$

This actually means that in a comparison between patients from different groups at the same time, it is expected that on average the MMSE score of the not neuro-psychiatric group is 9.11 units above the other group. In fact, given the significance of this estimate, it can be concluded that this difference is statistically significant.

Now, in order to verify if the model is accurate and conclusions are reliable, is also important to check how good is the variance structure estimated. To do this, an ANCOVA model with the same fixed-effects is fitted, to obtain the observed covariance and correlation matrix. Then a comparison between the observed and the fitted variance of the response variable is conducted and shown in Figure 6. Evidently, there is a lack of fit due to the fact that the observed variance has an almost cubic behavior while the estimated function follows a linear trend.

Considering this, a quadratic term for the logarithm of time is included in the random part of the model to make the covariance structure closer to what is observed. When a higher order term is included in the random part of the model, the variance of the response variable is estimated through a higher degree polynomial. Specifically, adding the square of the logarithm of time, implies that the variance is estimated through a four degree polynomial.

By doing so, the estimation of the variance of the squared of the logarithm of time is zero. Hence, the estimation of the variance of the response variable is affected in an unexpected way (see Figure 7).

Having a zero variance in one of the components of the random-effects suggests that the likelihood could be further increased by allowing negative estimates for that

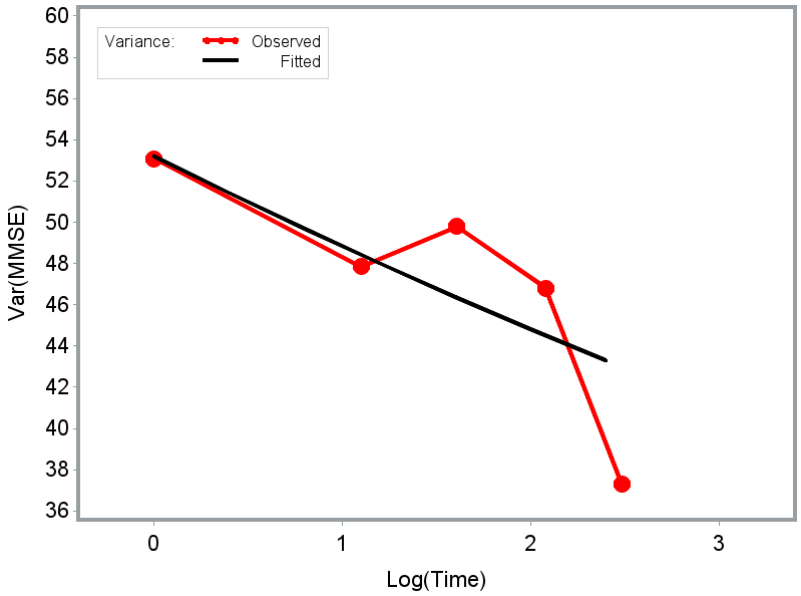


Figure 6: Comparison of variance function from model (2)

component. By default, SAS does not allow the estimation of negative variances, but it can be changed by adding the option NOBOUND to the proc mixed. As a consequence, the variance estimate is not zero anymore, but it does not lead to any improvement in the fit of the variance of the response variable (see Figure 8). In any case, it makes it even worst.

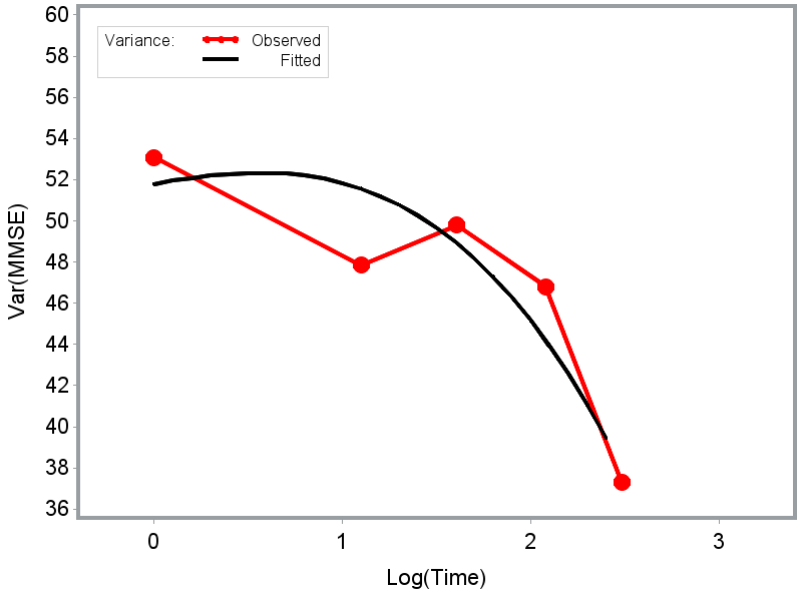


Figure 7: Comparison of variance function from model (2) with log_time squared

Furthermore, it is important to highlight what Brown and Prescott (2015) said about negative variance components. They said that "if a variance component is negative, the usual action would be either to remove the corresponding random effect from the model

or to fix the variance component at zero.... If the random effect does not form part of the study design, then there is more reason to justify removing it from the model".

Therefore, model 2 is considered as the most appropriate structure, even though the lack of fit in the variance structure suggests that additional information should be considered to explain the evolution of the patients besides time.

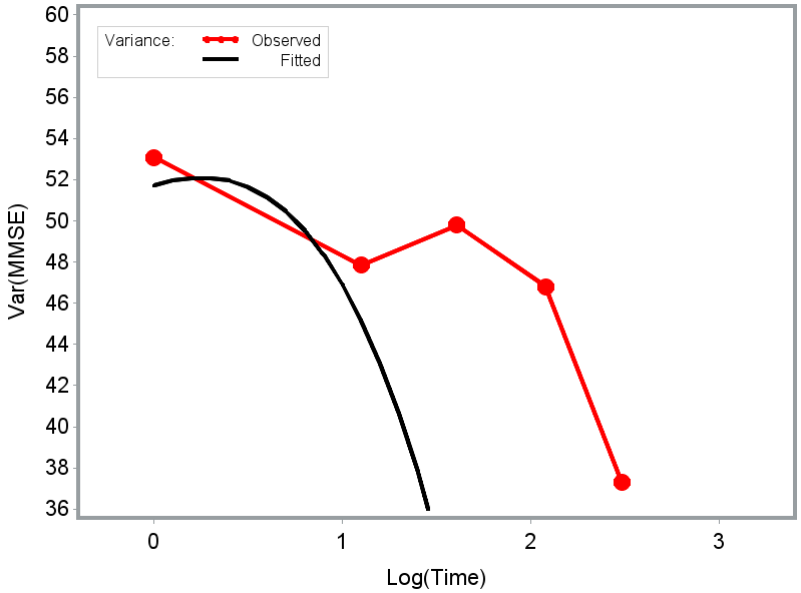


Figure 8: Comparison of variance function from model (2) with log_time squared, allowing negative variances

Following this, it is of interest to know how is the relationship of the random-effects for each patient. From the estimates of the variance components mentioned before, the estimation of the correlation between intercepts and slopes is -0.8072. So in order to illustrate this negative correlation, Empirical Bayes (EB) approach is used to get estimates of the $b_i's$ for each patient (see Figure 9). Such a strong correlation indicates that the evolution of a patient highly depends on how his score was in the beginning of the study. For instance, patients who had low MMSE scores on day one, tend to have larger slopes than patients who had higher MMSE scores.

In fact, one of the characteristics of this scatterplot is that allow to describe in detail how different is the evolution of patients. To give an example, patient number 10 stands out for having the smallest intercept (-17.43) and the largest slope (0.76). What makes him or her special, is that its measures are relatively low compared to the scores that other patients have in the same group, namely not neuro-psychiatric, making him or her an outlier profile in this group.

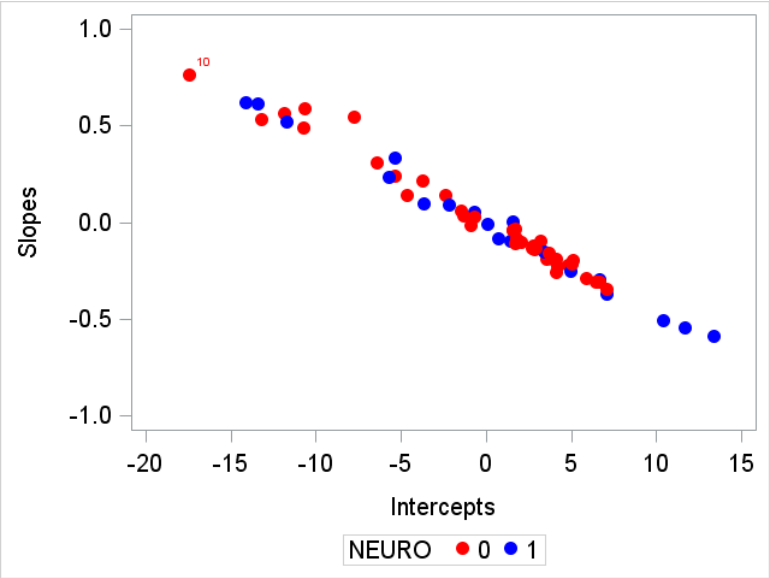


Figure 9: Random Intercepts vs Slopes

Now, in order to correct for important baseline differences between patients and improve the fit, the fixed part is modified by including the age of the subject, its housing situation and an interaction between these factors. The interaction between the logarithm of time and housing is also added because it is of interest to test whether there are differences between housing situation. The interaction between the logarithm of time and the groups is again added, because the addition of these new factors may change its behaviour.

In regard to age and housing, it is important to acknowledge two aspects of the data management. First, there are 5 patients in the study that do not have information with respect to their housing situation, and so they are excluded from this analysis. Second, the variable age is centered around its mean (Age_c) for a more practical interpretation of the fixed-effects. This study is based on elderly patients so a value of zero in age does not make much sense.

As a result, all main effects are significant in contrast to the interactions considered. Each interaction is therefore removed at a time from the model to see whether the exclusion of each term changes the significance of the other interaction. In the end, all interactions are removed, setting the following model:

$$Y_{ij} = \begin{cases} (\beta_{10} + b_{0i}) + (\beta_1 + b_{1i})ln(time_{ij}) + \beta_2 Age_{ci} + \beta_3 Housing_i + \epsilon_{ij} & \text{if Not neuro-psychiatric} \\ (\beta_{20} + b_{0i}) + (\beta_1 + b_{1i})ln(time_{ij}) + \beta_2 Age_{ci} + \beta_3 Housing_i + \epsilon_{ij} & \text{if Neuro-psychiatric} \end{cases} \tag{3}$$

Where all parameters are as described before, and β_2 and β_3 represent the effect of age and housing situation in the expected MMSE score. Note that housing is a categorical variable that can be expressed through dummy variables taking the category living in a nursing home as reference. For simplicity, it is shown here as a regular variable.

The fit of model 3 indicates that the new variables are highly significant to describe the evolution of MMSE score in the patients. Table 5 shows the estimations for each parameter.

	Estimate	**Std. Error**
Fixed-effects		
Intercept	11.97	1.57
Housing:Alone	5.31	2.02
Housing:With family	3.81	2.03
Age_C	-0.37	0.09
Ln(Time)	0.79	0.2
Not Neuro	5.96	1.66
Random-effects		
Var(Intercepts)	28.91	
Var(Slopes)	0.15	
Cov(Int,Slopes)	-1.57	
Var(Error)	6.26	

Table 5: Parameter estimations of model (3)

The variance structure changes a lot in comparison with model (2). The variability between intercepts is now 28.91, a difference of 18.32 units compared to the previous model. So including the variables age and housing is accounting some of the variability, that in the previous model was attributed to the own-subject evolution. The variance of the slopes is now 0.15, representing just a difference of 0.02 units with respect to model (2). Once again, the covariance between these two terms is negative (-1.57), leading to a negative correlation of -0.75.

Regarding the fixed-effects, the average MMSE score, at the start of the study, of a patient that has the average age, lives in a nursing home and belongs to the neuro-psychiatric group is 11.97. A patient that has the same conditions of age and housing situation, but belongs to the not neuro-psychiatric, has on average $11.97 + 5.96 = 17.93$ units at the beginning of the study. The age effect indicates that an increase of one year in the age of a patient leads to an average decrease of 0.37 units in MMSE, no matter the group the patient belongs to. In regard to the housing situation, the results suggest that on average a patient who lives alone, has 5.31 MMSE units more than a patient who lives in a nursing home, under the same situations, namely same age and measures taken on the same day. In comparison, a patient who lives with his or her family or partner has on average 3.81 MMSE units more that a patient who lives in a nursing home, under the same conditions. Finally, the effect of time suggests that an increase of one unit in the logarithmic timescale, leads to an average increase of 0.79 units in the MMSE score, no matter the group a patient belongs to. So the average evolution of MMSE in each group is given by:

$$E(Y_{ij}) = \begin{cases} 23.23 + 0.79time - 0.37Age_c & \text{if Not neuro-psychiatric and Housing:Alone} \\ 21.74 + 0.79time - 0.37Age_c & \text{if Not neuro-psychiatric and Housing:Family} \\ 17.93 + 0.79time - 0.37Age_c & \text{if Not neuro-psychiatric and Housing:Nursing} \\ 17.28 + 0.79time - 0.37Age_c & \text{if neuro-psychiatric and Housing:Alone} \\ 15.78 + 0.79time - 0.37Age_c & \text{if neuro-psychiatric and Housing:Family} \\ 11.97 + 0.79time - 0.37Age_c & \text{if neuro-psychiatric and Housing:Nursing} \end{cases}$$

This means that in a comparison between patients from different groups at the same time, it is expected that on average the MMSE score is higher on not neuro-psychiatric regardless their housing situation. In fact, given the significance of this estimate, it can be concluded that this difference is statistically significant.

In regard to the differences between housing situations, is concluded that in the beginning of the study, these differences are significant. On the other hand, the slopes, measured through the interaction with the logarithm of time, are not significantly different resulting in all groups with the same slopes.

In order to be completely sure about these conclusions, is important to check how good is the estimation of the variance structure. An ANCOVA model with age and housing is fitted to obtain the observed covariance matrix. The comparison is done again between the observed and fitted variance of the response variable (see Figure 10).

It is evident that a linear function is not enough to estimate the variance, and for this model the cubic trend in the observed variance is even more evident. Hence, a higher degree polynomial is considered.

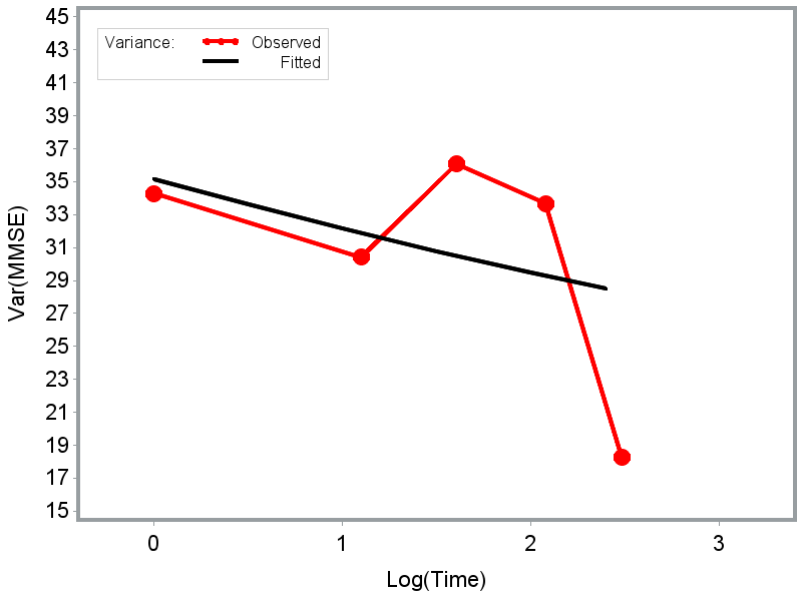


Figure 10: Comparison of variance function from model (3)

As in the previous model, a quadratic term for the logarithm of time is included in the random part of the model to make the covariance estimate more flexible. Again,

the estimation of the variance of this new term is zero, suggesting that the likelihood could be further increased by allowing negative estimates for that variance. In SAS this restriction is removed and the model is fitted again. As a consequence, the variance is negative, but there is not improvement in the fit compared to the model that has zero variance for the square of the logarithm of time (See Figures 11 and 12).

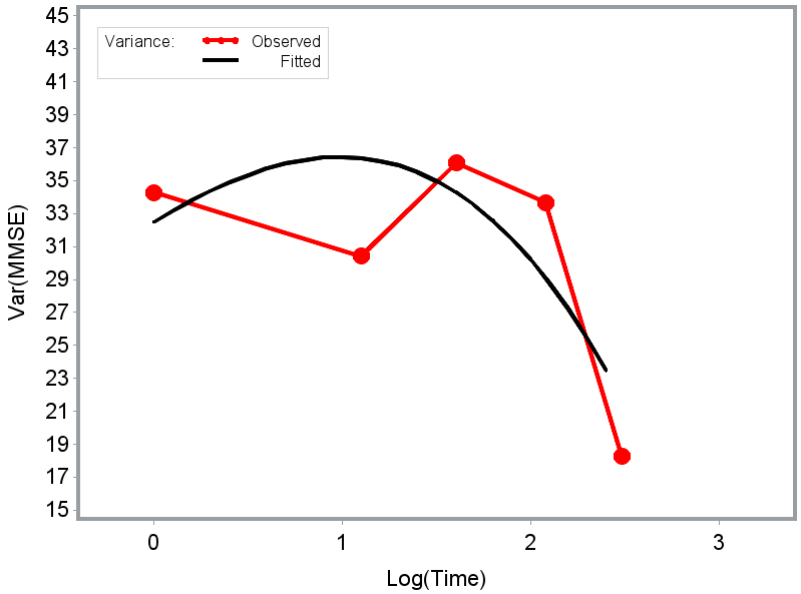


Figure 11: Comparison of variance function from model (3) with log_time squared

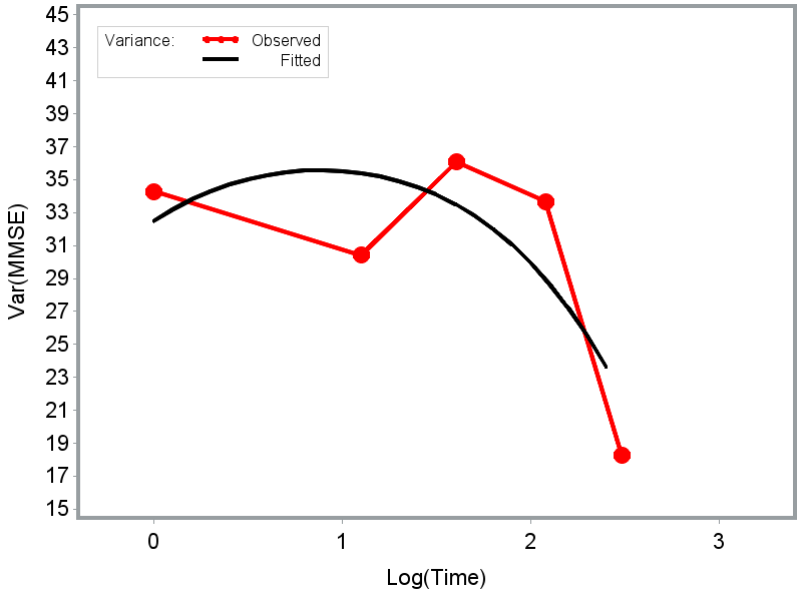


Figure 12: Comparison of variance function from model (3) with log_time squared, allowing negative variances

In this context, two choices can be made regarding the fit of the variance structure. First, take what Brown and Prescott (2015) said about negative variances and leave the final model with just the linear trend. Second, include a cubic term in the random

part to improve the fit. It is very clear that the linear structure fitted is not enough so the later options is considered.

To do so, the cubic term of the logarithm of time is added to the random part of the model. Hence, the model can be expressed as:

$$\begin{aligned} Y_{ij} = (\beta_{10} + b_{0i}) + (\beta_1 + b_{1i})ln(time_{ij}) + b_{2i}ln(time_{ij})^2 + b_{3i}ln(time_{ij})^3 + \\ \beta_4 Age_{ci} + \beta_5 Housing_i + \epsilon_{ij} \end{aligned} \tag{4}$$

Note that in this model, there are four random terms: three random slopes and one random intercept. Therefore, it is assumed that these random-effects are normally distributed with mean zero and covariance matrix **D**. This covariance matrix can be expressed as:

$$\mathbf{D} = \begin{bmatrix} d_{11} & d_{12} & d_{13} & d_{14} \\ d_{12} & d_{22} & d_{23} & d_{24} \\ d_{13} & d_{23} & d_{33} & d_{34} \\ d_{14} & d_{24} & d_{34} & d_{44} \end{bmatrix}$$

Where the diagonal is the variance of the intercept, the logarithm of time, the square of the logarithm of time and the cubic of the logarithm of time, respectively.

The estimation of the variance of the response variable is obtained as follows:

$$\begin{aligned} Var(Y_{ij}) &= Var\big[(\beta_{10} + b_{0i}) + (\beta_1 + b_{1i})ln(time_{ij}) + b_{2i}ln(time_{ij})^2 + b_{3i}ln(time_{ij})^3 + \\ &\qquad \beta_4 Age_{ci} + \beta_5 Housing_i + \epsilon_{ij}\big] \\ &= Var\big[b_{0i} + b_{1i}ln(time_{ij}) + b_{2i}ln(time_{ij})^2 + b_{3i}ln(time_{ij})^3 + \epsilon_{ij}\big] \\ &= d_{44}ln(time_{ij})^6 + 2d_{34}ln(time_{ij})^5 + d_{33}ln(time_{ij})^4 + 2d_{24}ln(time_{ij})^4 + \\ &\quad 2d_{23}ln(time_{ij})^3 + d_{22}ln(time_{ij})^2 + 2d_{14}ln(time_{ij})^3 + 2d_{13}ln(time_{ij})^2 + \\ &\quad 2d_{14}ln(time_{ij}) + d_{11} + \sigma_\epsilon^2 \end{aligned}$$

The comparison between the fitted and the observed variance is displayed in Figure 13. The fitted variance is now closer to the observed variance when the measures were taken. There is still an under-representation between the first and the second measure, but the overall fit is much better than the linear fit. For this reason, this model is considered to give the final conclusions.

The estimation of the fixed-effects of model (4) does not change much compared to the previous model where only the random intercepts and slopes were considered (model 3). The conclusions are the same in the sense that all terms in the fixed part are significant, but the point estimation of each coefficient changes a little bit (see Table 6).

The average MMSE score, at the start of the study, of a patient that has the average age, lives in a nursing home and belongs to the neuro-psychiatric group is 12.03. A patient that has the same conditions of age and housing situation but belongs to the not neuro-psychiatric, has on average $12.03 + 5.79 = 17.82$ units at the beginning of the study. The age effect indicates that an increase of one year in the age of a patient leads to an average decrease of 0.43 units, no matter the group the patient belongs to. In regard to the housing situation, the results suggest that on average a patient who lives alone has 5.75 MMSE units more than a patient who lives in a nursing home,

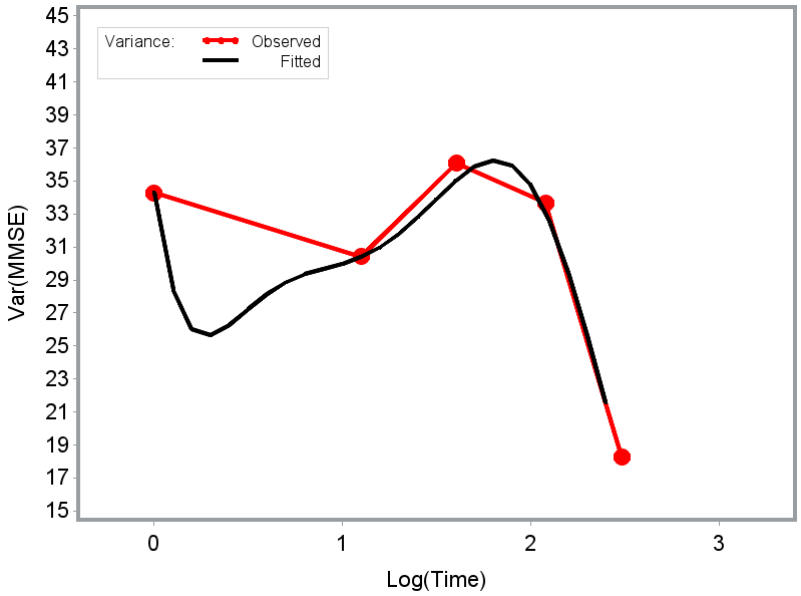


Figure 13: Comparison of variance function from model (4)

	Estimate	**Std. Error**
Fixed-effects		
Intercept	12.03	1.38
Housing:Alone	5.75	1.79
Housing:With family	4.27	1.81
Age_C	−0.43	0.08
Ln(Time)	0.61	0.17
Not Neuro	5.79	1.50
Random-effects		
See Table 7		
Var(Error)	6.26	

Table 6: Parameter estimations of model (4)

under the same situations, namely same age and measures taken on the same day. In comparison, a patient who lives his or her family or partner has on average 4.27 MMSE units more than a patient who lives in a nursing home, under the same conditions. Finally, the effect of time suggests that an increase of one unit in the logarithmic time scale, leads to an average increase of 0.61 units in the MMSE score, no matter the group a patient belongs to. So the average evolution of MMSE in each group is given by:

$$E(Y_{ij}) = \begin{cases} 23.57 + 0.61time - 0.43Age_c & \text{if Not neuro-psychiatric and Housing:Alone} \\ 22.09 + 0.61time - 0.43Age_c & \text{if Not neuro-psychiatric and Housing:Family} \\ 17.82 + 0.61time - 0.43Age_c & \text{if Not neuro-psychiatric and Housing:Nursing} \\ 17.78 + 0.61time - 0.43Age_c & \text{if neuro-psychiatric and Housing:Alone} \\ 16.30 + 0.61time - 0.43Age_c & \text{if neuro-psychiatric and Housing:Family} \\ 12.03 + 0.61time - 0.43Age_c & \text{if neuro-psychiatric and Housing:Nursing} \end{cases}$$

Regarding the estimation of the random-effects, there are now more parameters because of the inclusion of higher order terms (see Table 7). The variance of the slope of logarithm of time is huge compared to the previous model (see Table 5), this is a consequence of having a more complex structure in the random part of the model. However, what matters most is how the variance of the response variable is fitted and in this case it is much better than before.

	$Intercept$	$ln(time)$	$ln(time)^2$	$ln(time)^3$
$Intercept$	30.47	-41.4	44.61	-12.07
$ln(time)$	-41.4	185.5	-183.64	46.51
$ln(time)^2$	44.61	-183.64	183.89	-46.85
$ln(time)^3$	-12.07	46.51	-46.85	11.97

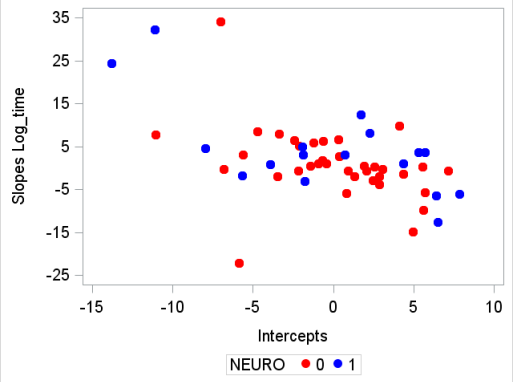
Table 7: Fitted Covariance Matrix from model (4)

The associations between the random effects are a consequence of the estimation of this covariance matrix. Figure 14 shows how strong is the correlation between these random-effects. Note that the log-time terms are as expected, almost perfectly correlated.

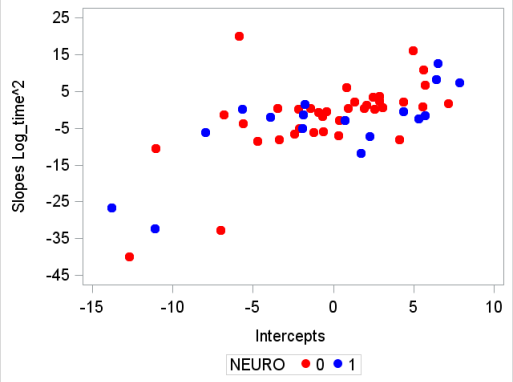
In addition, the EB estimations are useful to identify outlying behaviours in the data. In particular, histograms of the random effects regarding log-time, lead to identify four patients with an atypical evolution (patients number 54, 53, 25 and 12). This can be seen in Figure 15, where there are frequencies that do not follow the general pattern.

After having identified which patients could be considered as outliers, this is found:

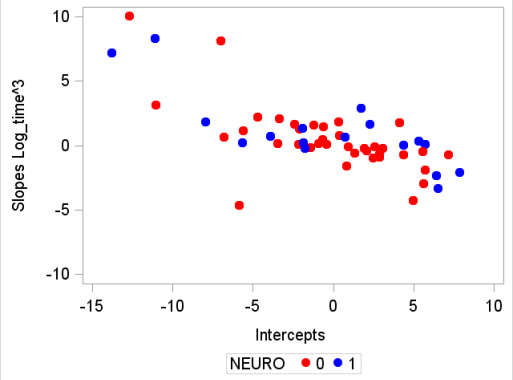
- Number 54 is a not neuro-psychiatric patient of 79 years old that lives with his/her family/partner. Its MMSE measurements are 5, 20, 15 and 24. The most unusual pattern in his information is the first measurement, it is very low compared to its other measures. This could be the case of a typing error.
- Number 53 is neuro-psychiatric patient of 84 years old that lives with his/her family/partner. Its MMSE measurements are 0, 8, 0, 0 and 6. Its unusual behaviour is explained by being the lowest MMSE evolution in the entire sample.
- Number 25 is a neuro-psychiatric patient of 68 years old that lives alone. Its MMSE measurements are 9, 20, 19, 10 and 21. This patient stands out because its evolution is more variable compared with other patients.



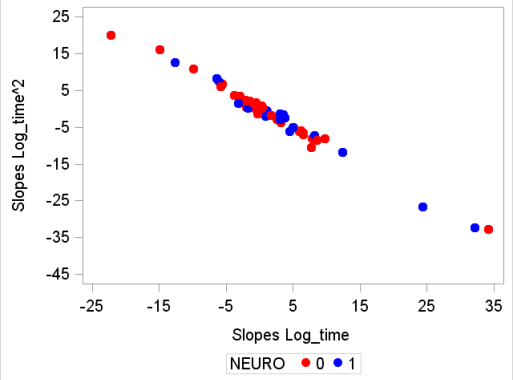
(a) Scatterplot Intercepts Vs Slopes Log-time



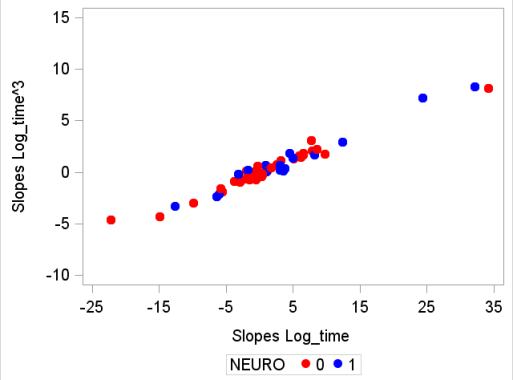
(b) Scatterplot Intercepts Vs Slopes $Log - time^2$



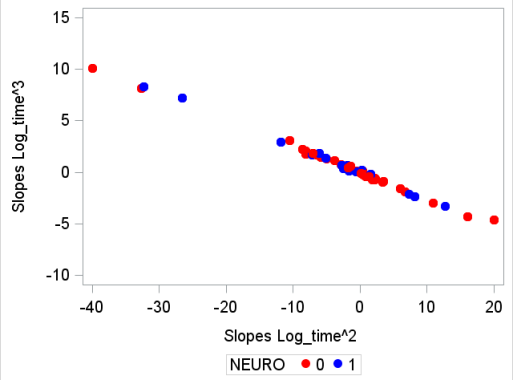
(c) Scatterplot Intercepts Vs Slopes $Log - time^3$



(d) Scatterplot Slopes Log-time Vs Slopes $Log - time^2$

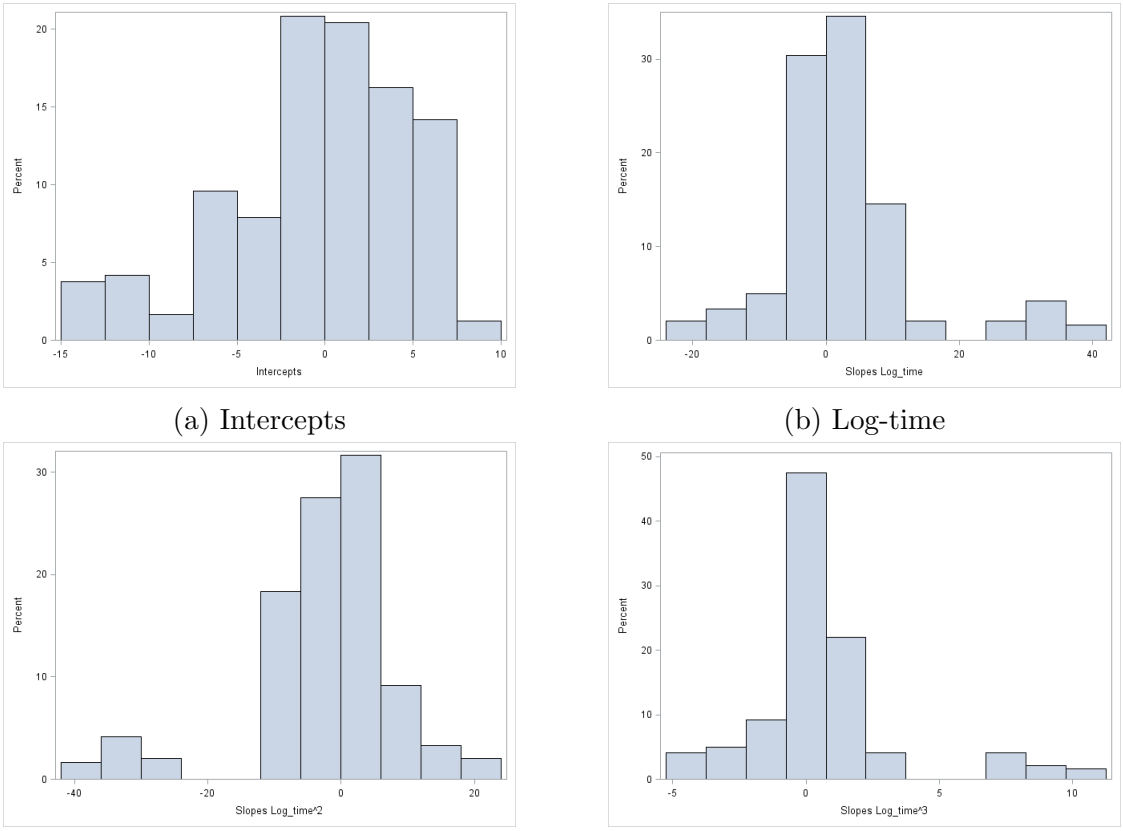


(e) Scatterplot Slopes Log-time Vs Slopes $Log - time^3$



(f) Scatterplot Slopes $Log - time^2$ Vs Slopes $Log - time^3$

Figure 14: Scatterplots random effects Model 4



(a) Intercepts

(b) Log-time

(c) $Log - time^2$

(d) $Log - time^3$

Figure 15: Histograms random effects Model (4)

- Number 12 is a not neuro-psychiatric patient of 86 years old that lives in a nursing home. Its MMSE measurements are 4, 20, 12, 13 and 17. What stands out in this patient are the big changes in scores at the beginning of the study.

To sum up, after having fitted the model to establish the evolution in the MMSE score and to determine the differences between neuro-psychiatric and not neuro-psychiatric group, the age of the patients and their housing situation are included in the model to control for possible differences at the beginning of the study. As a consequence, the point estimates of the fixed-effects and random-effects change. The random part of the model is the one that presents more differences because in this new model, the variance of the response variable can not be fitted correctly with a linear structure. For this reason, the square and the cubic of the logarithm of time are included, allowing them to have random slopes, which resuls in a better fit of the observed response variance. The conclusions are now more reliable because they are controlled by baseline differences in age and housing situation.

In order to give a different approach to the analysis, the response variable MMSE is dichotomized and a logistic random intercepts model is fit to compare the evolution of these new values. In the literature, scores greater than or equal to 24 points in the MMSE scale indicates normal cognition state. The scores that are below this cutoff value are classified in different stages of dementia (Mungas, 1991). In particular, the observed scores in the sample would suggest that most of the patients suffer from de-

mentia, so this cutoff value is not meaningful for them.

A broader analysis should be made considering that the entire sample consists of elderly subjects, where the MMSE scores tend to be lower. However, the information available and the lack of expertise do not represent the best tools to define the most appropriate classification.

As a consequence, a meaningful dichotomization of the variable MMSE is based on the mean profiles and the fixed effect estimates of the previous models. In this sense, it is suggested that a cutoff value of 18 creates a clear separation in the groups, where values below this number are a reflection of a severe cognitive state. Thus, an indicator variable is created from the MMSE scores as:

$$MMSE_d = \begin{cases} 1 & \text{if } MMSE < 18 \\ 0 & \text{if } MMSE \geq 18 \end{cases}$$

Figure 16 shows the evolution of this new variable for each group, where the proportions of patients with scores below 18 are plotted against time.

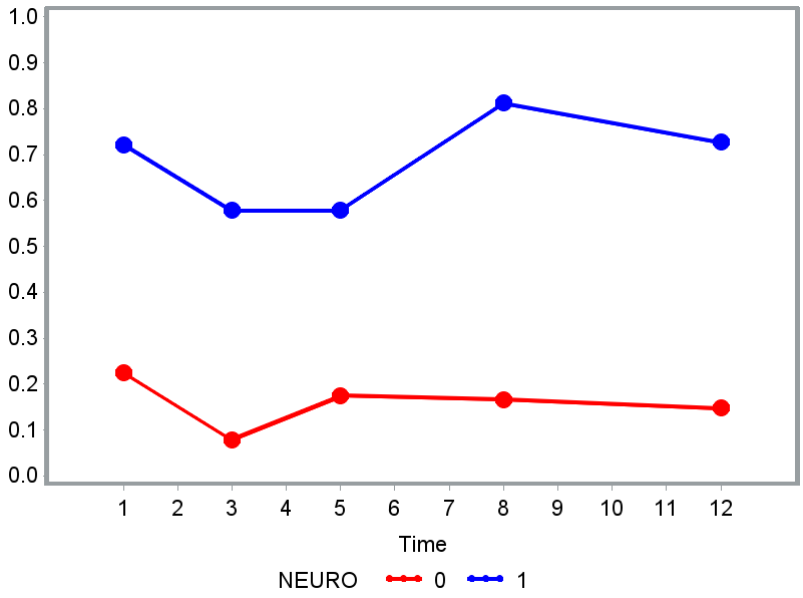


Figure 16: Proportion evolution

Once again, the proportion profiles show a well-defined separation between both groups over time. The not neuro-psychiatric group has a starting average proportion of patients with a score below 18 around 0.2 and finishes approximately in 0.15. On the contrary, the neuro-psychiatric starts and ends at 0.72, with some ups and downs in the measures. In comparison with the mean profiles of the continuous variable MMSE, the profiles are not so flat.

In detail, the evolution of the probability of having a MMSE under 18 points is modeled using a logistic approach, including a log-linear time trend and a group effect. The association given by the repeated measures for each subject is modeled including random intercepts. The model is defined as:

$$Y_{ij} \sim Bernoulli(\pi_{ij})$$

$$logit(\pi_{ij}) = log(\frac{\pi_{ij}}{1-\pi_{ij}}) = \begin{cases} (\beta_1 + b_i) + \beta_2 ln(time_{ij}) & \text{if Not neuro-psychiatric} \\ (\beta_3 + b_i) + \beta_4 ln(time_{ij}) & \text{if Neuro-psychiatric} \end{cases} \quad (5)$$

As in the continuous case, the interaction between the logarithm of time and the neuro-psychiatric status is included but is not significant. So the slope in the fixed part is the same for both groups, i.e., $\beta_2 = \beta_4$. Table 8 shows the estimations of this model.

	Estimate	**Std. Error**
Fixed-effects		
Intercept	1.3494	0.7387
Ln(Time)	−0.2750	0.2576
Not Neuro	−3.3757	0.8209
Random-effect	5.5079	

Table 8: Parameter estimations of model

Since model 5 is a Generalized Linear Mixed Model, the estimated values of the fixed effects cannot be interpreted as in the linear case. The fixed parameters have a marginal average and a subject specific evolution. As stated by Molenberghs and Verbeke (2006), these two kinds of evolution have a completely different interpretation. The marginal average expresses how, on average, the success probability evolves in the population. In contrast, the subject specific evolution models the expected evolution of a particular individual subject separately, which in this case is the average subject. Therefore, the marginal average evolution is derived from averaging simulations using the estimated random effects (see Figure 17), while the average subject evolution is obtained when the b_i's are set to zero ($b_i = 0$), see Figure 18.

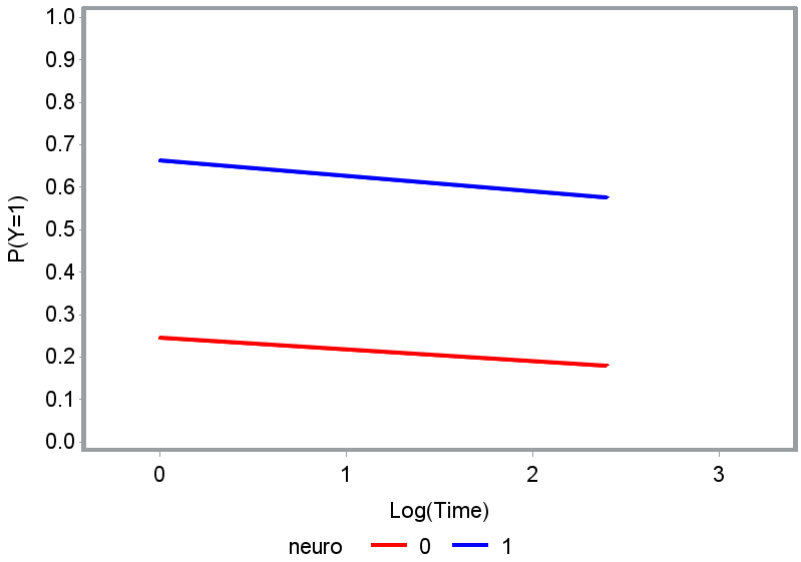


Figure 17: Marginal average evolution

In general, both plots show similar trends. Particularly, in the subject specific evolution the difference between the groups is larger than in the average of the population. This means, for the average subject the probability of having a score under 18 being neuro-psychiatric at log-time 1 is above 0.8 whereas for the a not neuro-psychiatric is about 0.1. And for the marginal average evolution, the neuro-psychiatric shows a probability of having score under 18 at log-time 1 of about 0.65, while in the not neuro-psychiatric group is about 0.22.

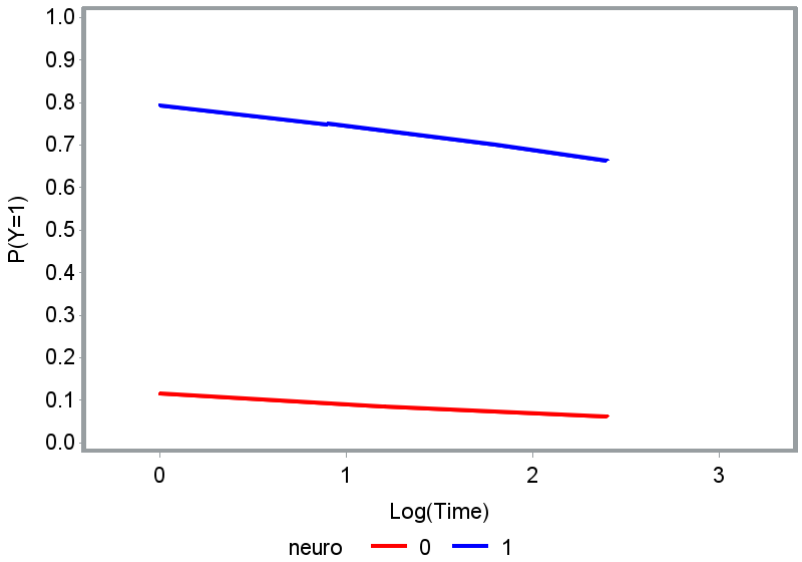


Figure 18: Evolution of average subject, with random effect zero

All in all, both evolutions follow the same trend, where the proportion of patients in a severe state decreases over time. The results are consistent with the linear case, where the MMSE score increases over time.

As before, the base-line variables age and housing are added to model with the same technical considerations (missing values are not analyzed and the age is centered). Considering this, the proposed model is:

$$Y_{ij} \sim Bernoulli(\pi_{ij})$$

$$\begin{aligned} logit(\pi_{ij}) &= log(\frac{\pi_{ij}}{1-\pi_{ij}}) \\ &= \begin{cases} \beta_1 + b_i + \beta_2 ln(time_{ij}) + \beta_5 Age_{ci} + \beta_6 Housing_i & \text{if Not neuro-psychiatric} \\ \beta_3 + b_i + \beta_4 ln(time_{ij}) + \beta_5 Age_{ci} + \beta_6 Housing_i & \text{if Neuro-psychiatric} \end{cases} \end{aligned} \tag{6}$$

The estimation of this model can be seen in Table 9.

	Estimate	Std. Error
Fixed-effects		
Intercept	2.5433	1.0222
Ln(Time)	−0.3558	0.3050
Not Neuro	−3.3405	1.1471
Age_c	0.2379	0.07961
Living Alone	−2.4570	1.1885
Living with family	−2.1554	1.1724
Random-effect	5.0717	

Table 9: Parameter estimations of model

It is important to acknowledge how in the binomial case, including baseline variables in the fixed part does not have a large impact in the variance component. This result can be associated with the fact of having a simpler variance function (linear) because the random part is composed only by subject specific intercepts. Therefore, the estimated variability between subjects is close to the estimation in the previous model.

In order to interpret the fixed estimates of the model, the marginal average evolutions and the evolution of the average subject are used (see Figures 19 and 20). Due to the presence of new covariates, the evolutions are compared for the average age in the sample and a combination of the group and housing situation is used to interpret their fixed effects. Thus, in the evolution plots the combination is described by the group-housing combination (NH), where the level 0 represents the not neuro-psychiatric group and living alone, level 1 as not neuro-psychiatric group and living with family or partner, level 2 for the not neuro-psychiatric group and living in nursing home, level 3 for the neuro-psychiatric group and living alone, level 4 for the neuro-psychiatric group and living with family or partner, and level 5 for the neuro-psychiatric group and living in nursing home.

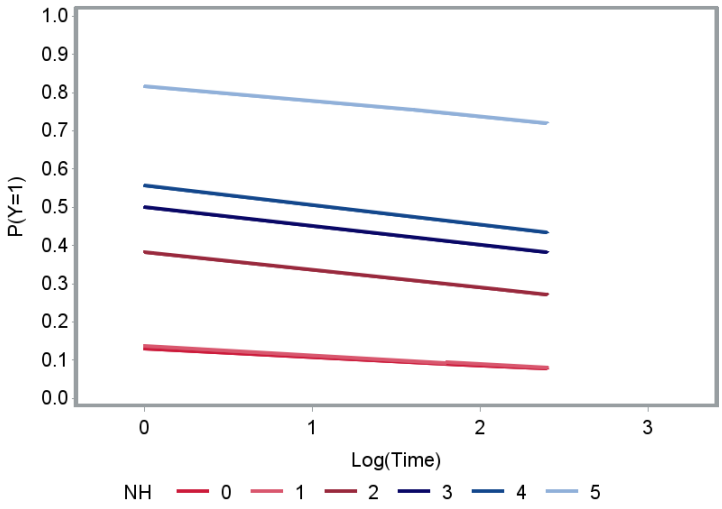


Figure 19: Marginal average evolution

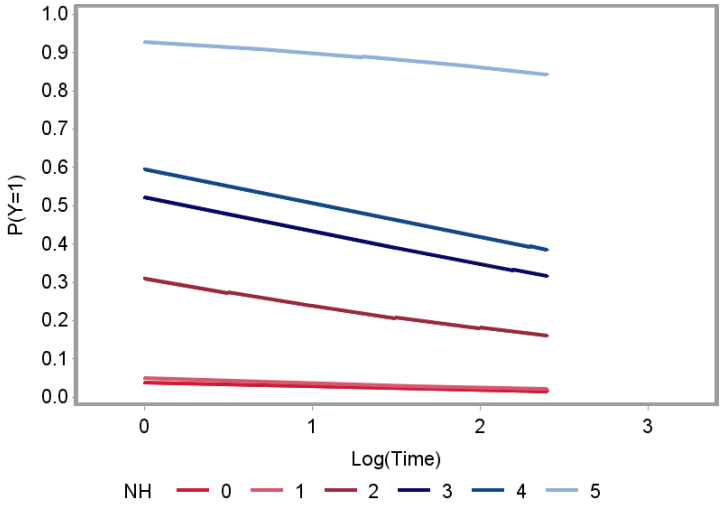


Figure 20: Evolution of average subject, with random effect zero

From both evolutions, is seing how the presence of a severe case is mostly influenced by the housing situation when the patient lives in a nursing home. Also, level 0 and 1 showed no difference at all, and the general trend of having a greater probability of severe cases is observed for the neuro-psychiatric group.

In summary, data from a sample of elderly patients that went through hip fracture surgery is analyzed to compare their MMSE evolution, considering their pre-operative cognitive status, age and housing situation. A mixed model approach is used given the longitudinal nature of the data.

First, a descriptive analysis showed differences between the evolution of the neuro-psychiatric groups, and the variability between subject profiles and variance structure suggest the model should include both random intercepts and slopes regarding the time.

As a consequence, a linear mixed model is fitted considering the time (in a logarithmic scale) and neuro group as predictors in the fixed part; and allowing subject specific intercepts and slopes regarding the time evolution in the random part. The average evolution of MMSE score showed significant differences between the neuro groups, where the predicted evolution of the not neuro psychiatric group was higher than the neuro-psychiatric over time.

In addition, due to the lack of fit of the variance structure, a quadratic logarithm time term is included as a random slopes effect, with no improvement to the fit. Thus, the linear variance structure is kept. The correlation between the EB estimates of the intercepts and slopes is estimated as highly negative, suggesting that patients who had low MMSE scores on day one, tend to have larger slopes than patients who had higher MMSE scores at the beginning of the study.

Furthermore, variables age and housing are included in the model to improve it, resulting in the decrease of the estimated variance for the random intercepts because these new variables are accounting some of the explained variability. As for the fixed

effects, it is found that patients living alone or with their family/partner tend to have on average higher MMSE score than the ones who lived in a nursing home. For its part, the age effect suggests the average MMSE score decreases as the patient gets older. In regard to the random part of the model, quadratic and cubic log time slope terms are added, resulting in a meaningful improvement in the fit of the variance structure.

Finally, a dichotomization of the response variable is made to perform a Generalized Linear Mixed Model based on the previous results. The new variable defines being a severe case when the MMSE is below 18 units. As in the linear case, two models are fitted including time and neuro group and then adding baseline variables, but allowing only random intercepts; where conclusions are in the same direction as before.

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