

Concepts of multilevel, longitudinal, and mixed models: Group 3

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1 Introduction

The data set results from a longitudinal observational study, the aim of which is to study the post-operative evolution of the cognitive status of elderly hipfracture patients and their pre-operative cognitive status, and to study the effects of housing situation and age on these evolutions. The physical ability is measured using the MMSE (Mini Mental State Examination) score, with values between 0 and 30, where low values correspond to a bad cognitive condition, while high scores correspond to high cognitive condition of the patient. The pre-operative cognitive status is measured through the so-called ‘neuro-status’ which is a binary indicator for being neuro-psychiatric.

- id: patient identification number
- age: age of the patient at entry
- neuro: neuro-psychiatric status of the patient (1: neuro-psychiatric, 0: not neuro-psychiatric)
- mmse: MMSE score
- time: day after operation at which the MMSE score has been measured (1, 3, 5, 8, or 12)
- housing: the housing situation prior to the hip fracture (1: alone, 2: with family or partner, 3: nursing home)

2 Data exploration

Considering the completeness of the data, it can be observed that 5 persons’ housing situation is unknown. Additionally, there was some dropout over time as show in Table 1. The column “Nb” shows the number of respondent at each time instance. The column “Return” shows the number of respondents that participated at time t while they did not participate at time $t - 1$; there is, for instance, one respondent that did not

Table 1: Dropout and patient characteristics over time.

Time	Nb	Return	Dropout	Mean age	% neuro- psychiatric	Housing			
						%alone	%family/ partner	%nursing home	%NA
1	58	0	0	78.71	31.03	29.31	39.66	22.41	8.62
3	57	1	2	78.18	33.33	29.82	38.60	22.81	8.77
5	59	2	0	78.59	32.20	28.81	38.98	23.73	8.47
8	52	0	7	77.88	30.77	28.85	36.54	25.00	9.62
12	38	0	14	77.82	28.95	31.58	34.21	23.68	10.53

participate at $time = 1$ while he did participate at $time = 3$. The column “Dropout” shows the number of respondents that did not participate at time t while they did participate at time $t - 1$. It can be seen than many drop out at $time = 12$. The other columns show how the patient characteristics change over time as patients are added or lost from the study. Overall, there is not much variation which might indicate that the dropout of patients is not related to MMSE or patient characteristics. We will thus assume dropout is completely random.

Figure 1 shows the average evolution of MMSE over time (Loess curves) for groups of patients with different housing and/or neuro-psychiatric status. Patients that are not neuro-psychiatric seem to have higher MMSE that stays reasonably constant over time (except for nursing home patients). MMSE seems to go up over time for nursing home patients (but they are the smallest group), and down for neuro-psychiatric patients that live with their family or partner (or unknown housing). MMSE for neuro-psychiatric patients that live alone might have a quadratic evolution over time.

Figure 2 shows all patient profiles. There is quite a lot of variation between the patients’ evolution. The non-psychiatric patients are also under-represented (except in the nursing home group).

The last variable that is explored, is the age. The loess curves in Figure 3 show that age might be negatively correlated with MMSE.

2.1 Variance analysis and correlation structure

Figure 4 shows that the variance is larger for the neuro-psychiatric patients (the smallest group).

Figure 5 shows that there seems to be an inverse relationship between the mean mmse and the variance for patients with either neuro-psychiatric status.

2.2 Conclusion exploratory analysis

The exploratory analysis has shows that the pattern of mmse over time is likely not constant or even linear. One might attempt quadratic, cubic, or logarithmic transformations of time to accommodate this. Both the level (intercept) of mmse differs quite a lot, depending on neuro-psychiatric status, housing and age.

There seems to be high intraclass correlation???

3 Methodology and results

This section, gradually develops a statistical model that seems to fit the data best. It starts with a simple model where only limited covariates are included in 3.1

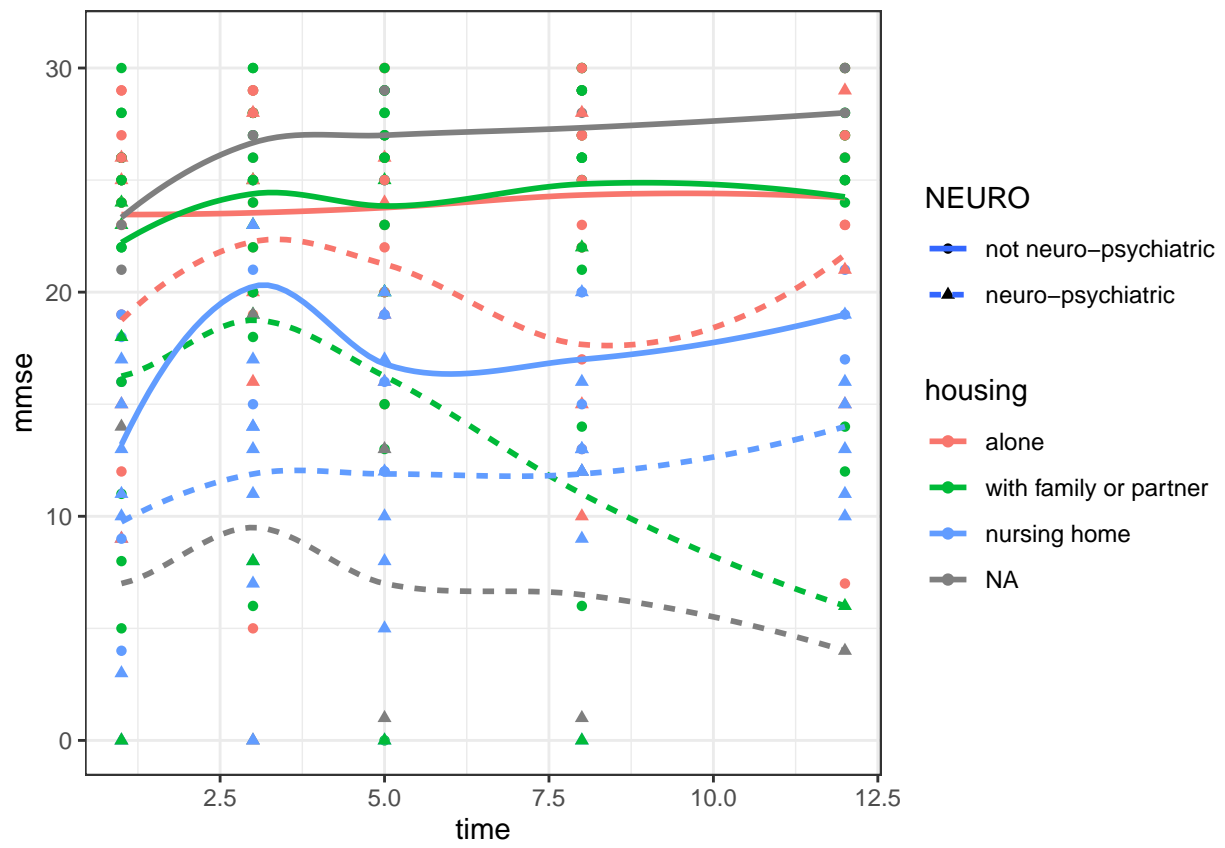


Figure 1: MMSE over time for all patient profiles, including smoothed curves.

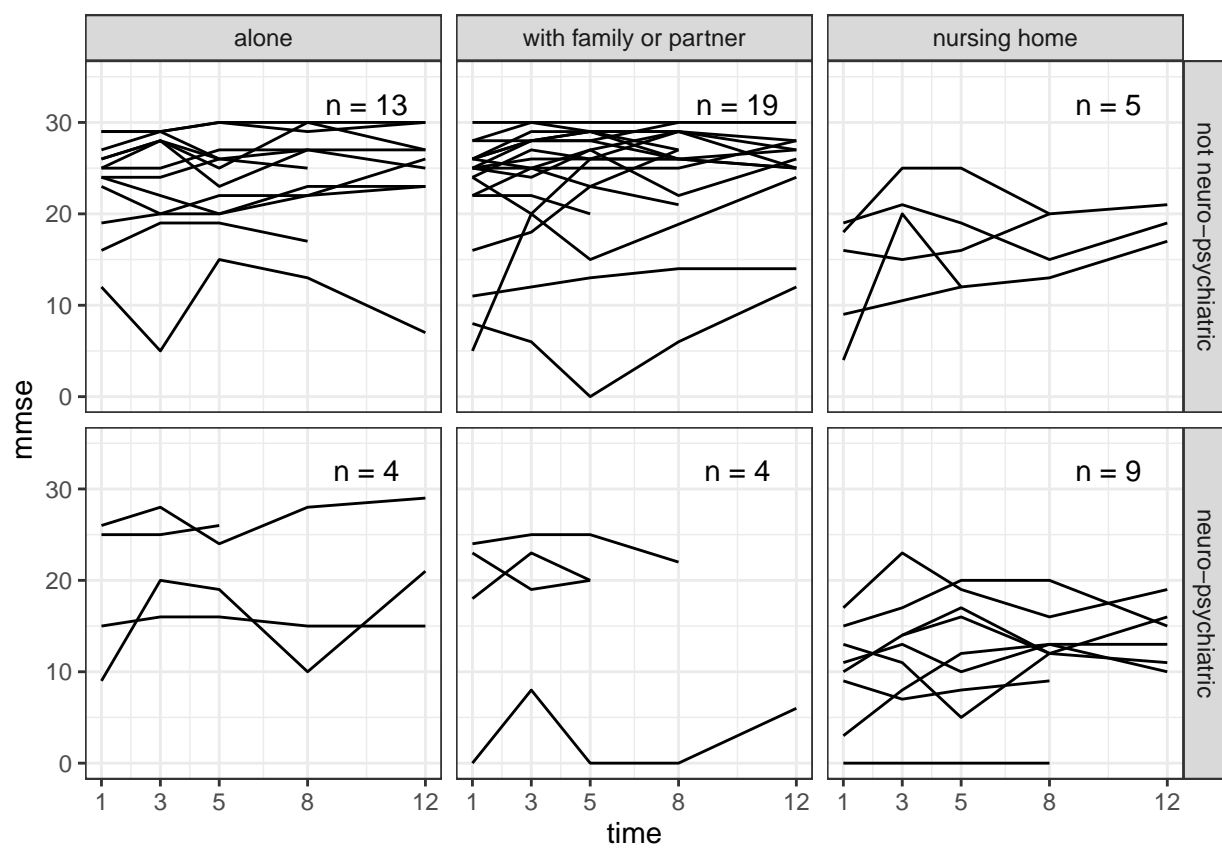


Figure 2: Patient profiles of MMSE over time.

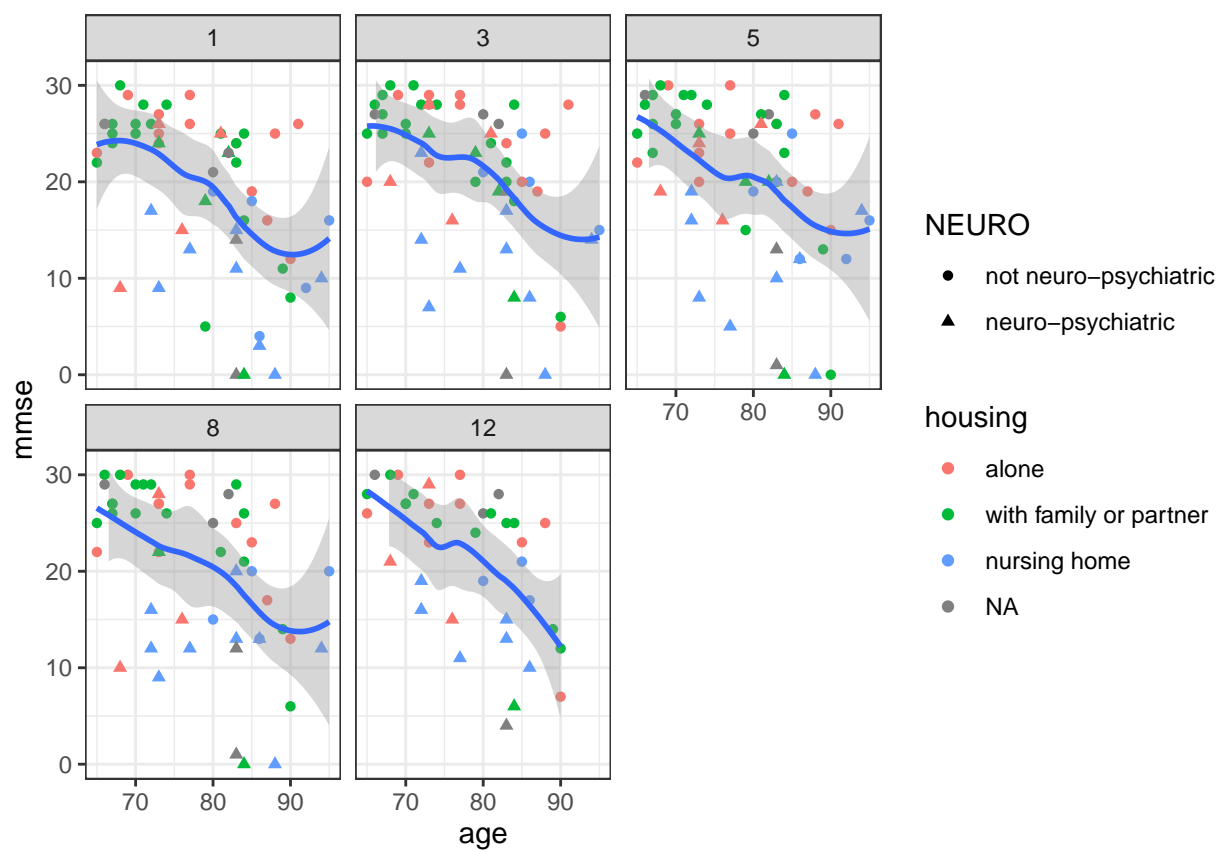


Figure 3: MMSE versus age. Facets show the time instances.

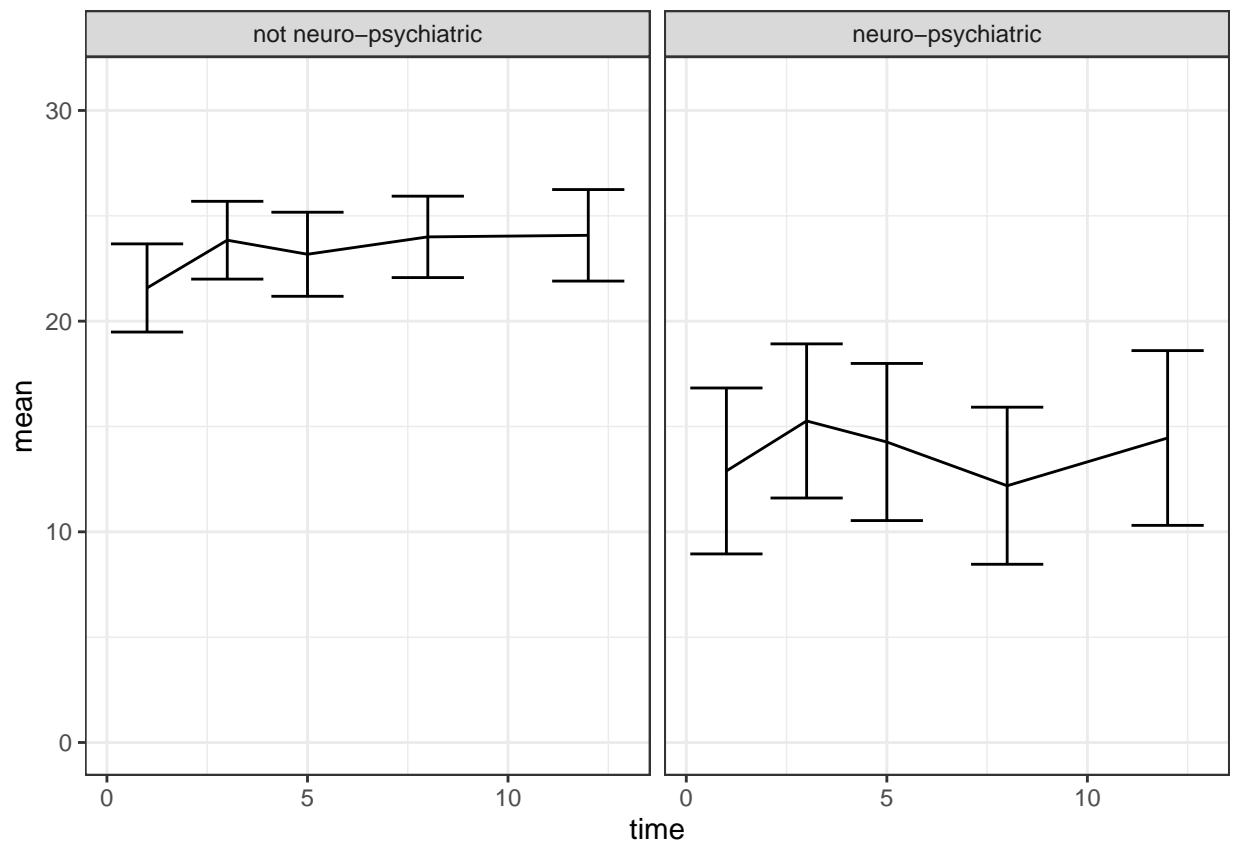


Figure 4: Error bars with 95 percent confidence intervals.

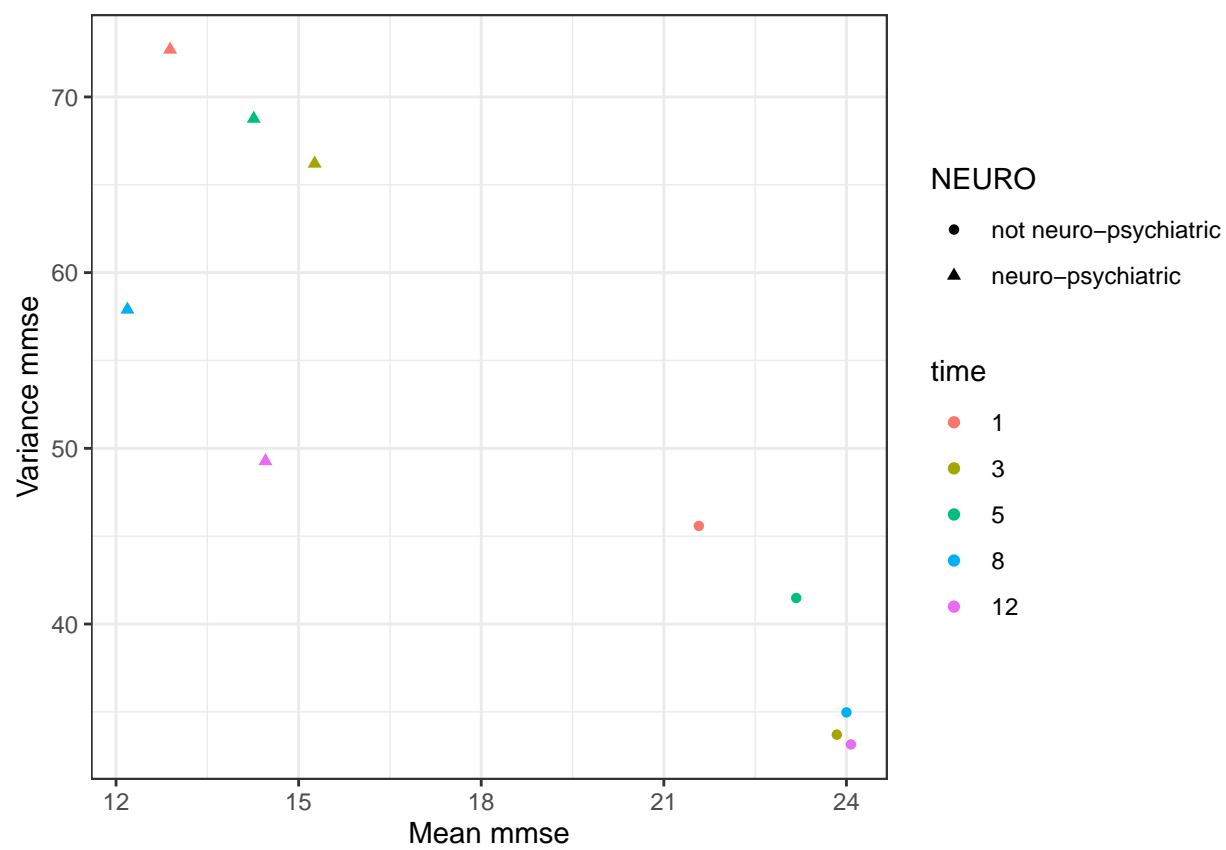


Figure 5: Variance and mean of the mmse, plotted for each of the groups.

Table 2: Fixed effects for the simple model with random intercept and slope

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	21.762	1.142	56.891	19.065	0.000
logtime	0.953	0.227	53.841	4.194	0.000
NEUROneuro-psychiatric	-8.381	2.016	57.314	-4.158	0.000
logtime:NEUROneuro-psychiatric	-0.327	0.415	57.976	-0.788	0.434

Table 3: variance-covariance matrix.

	(Intercept)	logtime
(Intercept)	47.383	-2.370
logtime	-2.370	0.203

3.1 A simple model

This first, simple model will assume a linear relationship between mmse and $\log(time)$ for each patient. The model allows for subject-specific intercepts and slopes and the neuro-psychiatric status is the only additional explanatory variable that is taken into account.

Table 2 shows the fixed effects for the simple model where time is on a log scale, with a random intercept and slope. For the average not-neuro-psychiatric patient, the slope is positive and the intercept is at 21.7624198. For the average neuro-psychiatric patients, the intercept is at 13.3817701 and the slope is less steep (as shown in Figure 7) but the difference in slope is not significant.

Figure 6 shows that the model performs reasonably well; there are no real remaining trends (all curves going up or down) and most residuals seem to randomly fluctuate around zero (no profiles are consistently above or below zero). There are, however, some individuals whose residuals are far larger (both positive and negative) than others.

Figure 8 shows the inverse relationship between the slope and the intercept: the higher the intercept, the lower the slope for each of the neuro-psychiatric statuses. This makes sense because MMSE is not a real continuous variable. It has a maximum value of 30 which means that there is less room for an increase in MMSE (meaning a lower slope) if the starting value (intercept) for MMSE is already high.

3.2 Model with housing and age

Before adding age to the model, it is centered around the mean (mean age is 78.28). Table 6 shows the results for the fixed effects. Non neuro-phsychiatric patients that are 78.28 years old and live alone are the baseline and have the highest intercept (23.12). For each increase in age of one year, the intercept is estimated to be 16.8659782 lower and neuro-psychiatric patients still have lower intercept and slope. Patients that live with family or partner have slightly lower intercept (not significant) than those who live alone. Patients that live in a nursing home have a significantly lower intercept than those who live alone. There is no significant difference in slope between neuro-psychiatric and non neuro-psychiatric patients.

Table 4: Standard deviations.

	x
(Intercept)	6.884
logtime	0.451

Table 5: Correlations.

	(Intercept)	logtime
(Intercept)	1.000	-0.764
logtime	-0.764	1.000

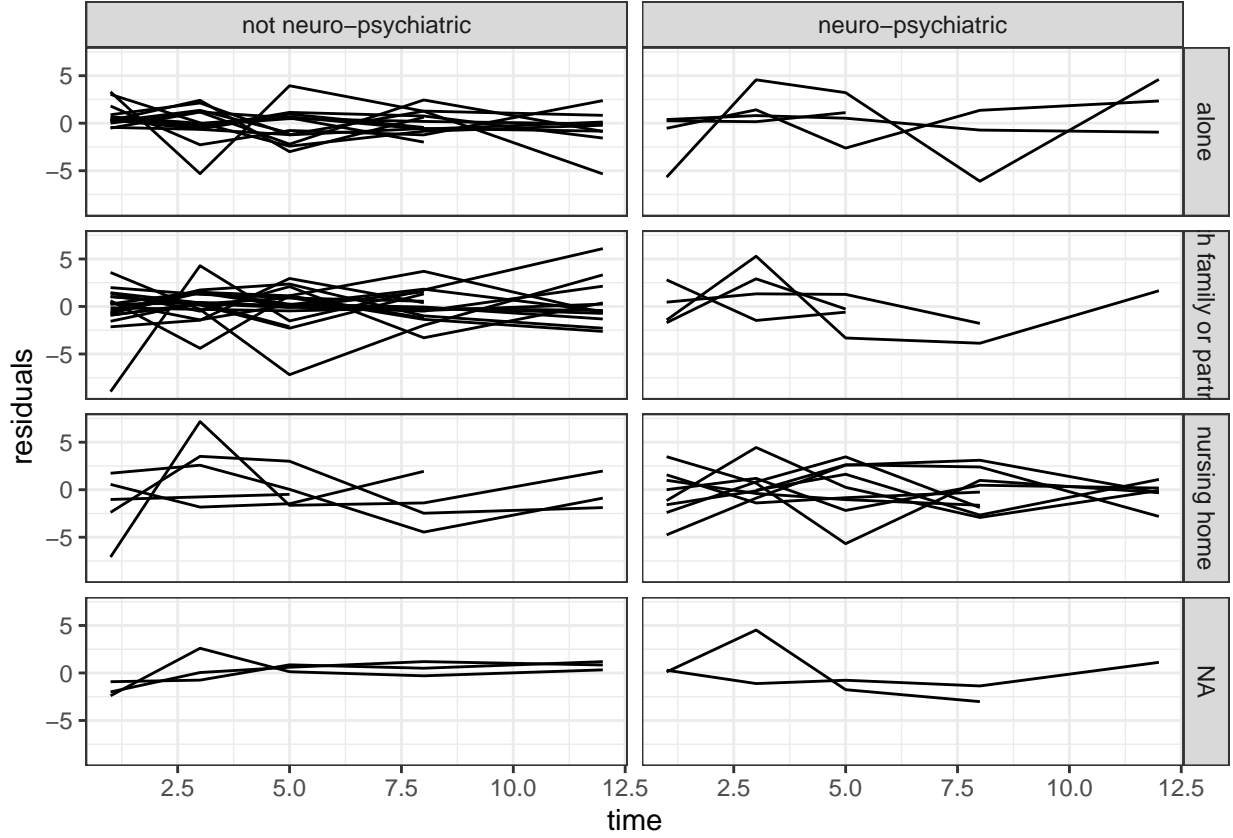


Figure 6: Residuals and time.

Table 6: Fixed effects for a model with random intercept and slope, including age and housing

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	23.123	1.371	56.189	16.866	0.000
logtime	0.851	0.243	49.821	3.508	0.001
NEUROneuro-psychiatric	-5.597	1.859	53.010	-3.010	0.004
agecenter	-0.368	0.090	49.306	-4.084	0.000
housingwith family or partner	-1.503	1.632	48.942	-0.921	0.362
housingnursing home	-5.282	2.020	49.305	-2.615	0.012
logtime:NEUROneuro-psychiatric	-0.194	0.447	53.060	-0.434	0.666

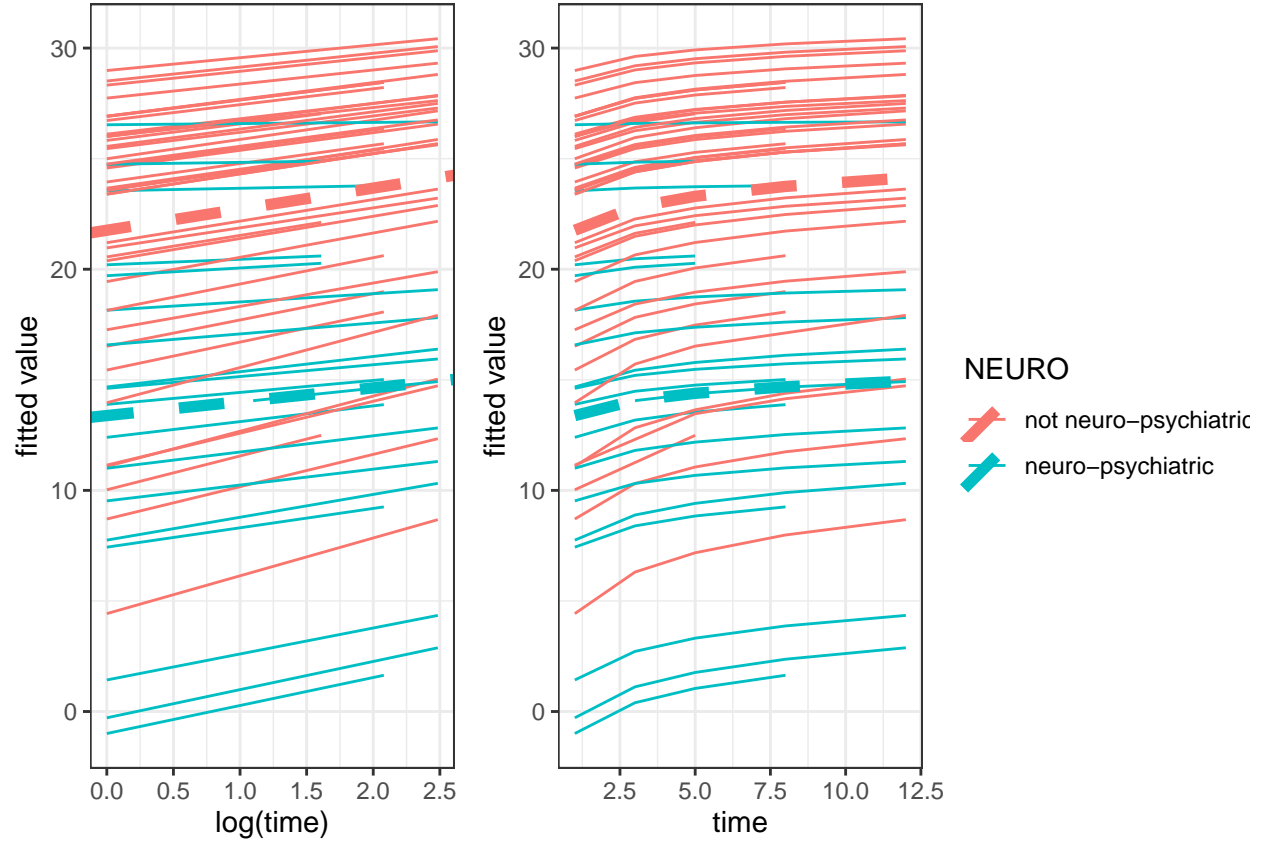


Figure 7: Fitted values plotted against $\log(\text{time})$ and time. Dashed, thicker lines are the predicted trends based on the fixed effects only, for each group.

Table 7: variance-covariance matrix.

	(Intercept)	logtime
(Intercept)	29.056	-1.665
logtime	-1.665	0.195

Table 8: Standard deviations.

	x
(Intercept)	5.390
logtime	0.442

Table 9: Correlations.

	(Intercept)	logtime
(Intercept)	1.000	-0.699
logtime	-0.699	1.000

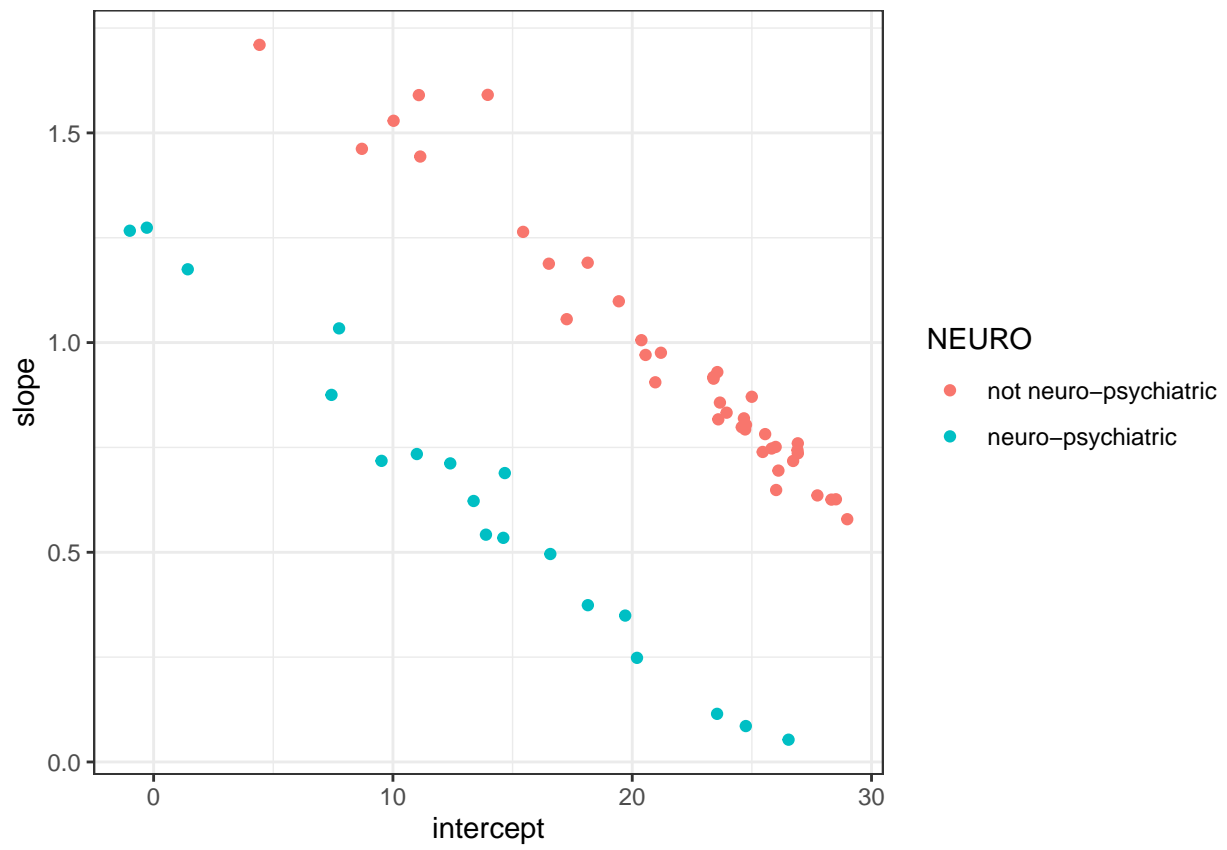


Figure 8: Scatterplot of the fitted intercept and slopes ($\log(\text{time})$).

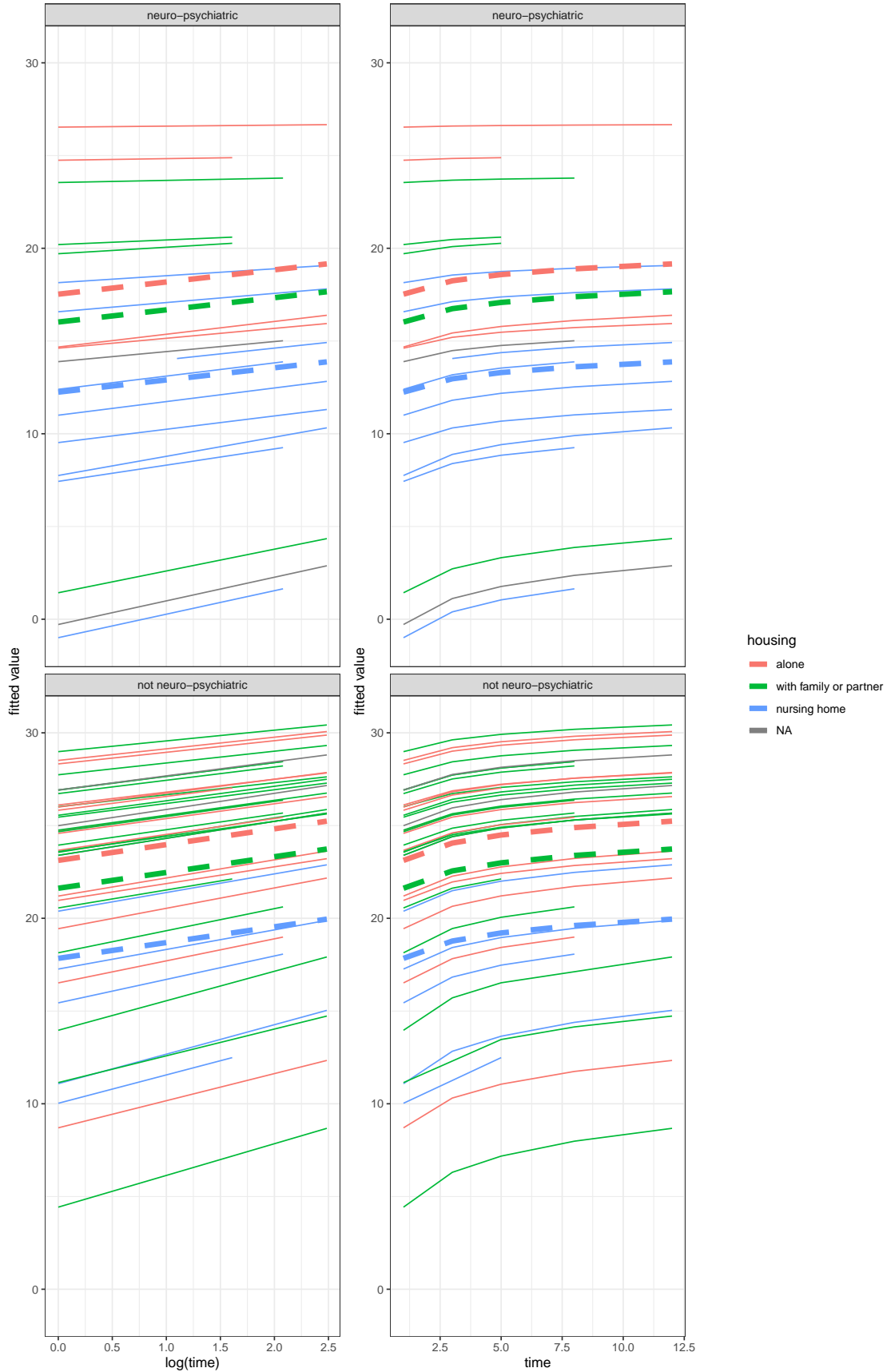


Figure 9: Fitted values plotted against log(time) and time. Dashed, thicker lines are the predicted trends based on the fixed effects only, for an average-aged patient in each group.

Table 10: Fixed effects for a model with random intercept and slope, including age and housing, dichotomized dependent variable (median split)

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	3.147	2.791	1.127	0.260
logtime	-0.071	0.594	-0.119	0.905
NEUROneuro-psychiatric	-7.879	4.302	-1.832	0.067
agecenter	-0.550	0.314	-1.752	0.080
housingwith family or partner	-0.801	3.036	-0.264	0.792
housingnursing home	-7.527	4.747	-1.586	0.113
logtime:NEUROneuro-psychiatric	-0.726	1.838	-0.395	0.693

Table 11: variance-covariance matrix.

	(Intercept)	logtime
(Intercept)	89.178	-14.967
logtime	-14.967	3.985

3.3 A model with a dichotomized dependent variable

3.3.1 Median split

Lastly, a model is tested where mmse is dichotomized using a median split; all mmse scores equal to or below the median (23) are categorized as “Low” and all mmse scores over 23 are categorized as “High”. It should be noted that the literature warns against this technique as it is rarely justified from either a conceptual or statistical perspective [maccallum2002practice].

In this model, nothing is significant. It seems we’ve indeed lost a lot of information by dichotomizing the dependent variable.

3.3.2 Dichotomized at 25

The maximum score for the MMSE is 30. A score of 25 or higher is classed as normal. If the score is below 24, the result is usually considered to be abnormal, indicating possible cognitive impairment.

In this model, nothing is significant. It seems we’ve indeed lost a lot of information by dichotomizing the dependent variable.

3.4 Checks Charlotte

Een model zoals pagina 31 kan ik niet fitten er zijn geen patienten met een normaal mmse bij de neuro-psychiatrische patienten in nursing homes.

Table 12: Standard deviations.

	x
(Intercept)	9.443
logtime	1.996

Table 13: Correlations.

	(Intercept)	logtime
(Intercept)	1.000	-0.794
logtime	-0.794	1.000

Table 14: Fixed effects for a model with random intercept and slope, including age and housing, dichotomized dependent variable (split at 25).

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	0.635	1.704	0.372	0.710
logtime	0.667	0.426	1.566	0.117
NEUROneuro-psychiatric	-5.639	3.050	-1.849	0.064
agecenter	-0.372	0.154	-2.414	0.016
housingwith family or partner	-0.192	1.889	-0.102	0.919
housingnursing home	-5.760	3.003	-1.918	0.055
logtime:NEUROneuro-psychiatric	-0.314	1.065	-0.294	0.768

Table 15: variance-covariance matrix.

	(Intercept)	logtime
(Intercept)	31.680	-3.716
logtime	-3.716	0.491

Table 16: Standard deviations.

	x
(Intercept)	5.628
logtime	0.701

Table 17: Correlations.

	(Intercept)	logtime
(Intercept)	1.000	-0.942
logtime	-0.942	1.000

Table 18: Model with random intercept and slope.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	13.3797900	1.6330108	8.1933260	0.0000000
logtime	0.6285619	0.3422532	1.8365404	0.0662778
NEUROinvnot neuro-psychiatric	8.3832482	1.9813380	4.2311046	0.0000233
logtime:NEUROinvnot neuro-psychiatric	0.3235940	0.4090749	0.7910386	0.4289215

Table 19: Model with random intercept and slope, including squared log(time).

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	13.2004775	1.6672767	7.9173888	0.0000000
logtime	1.3273264	0.6457149	2.0555920	0.0398219
logtimesquared	-0.3067081	0.2374284	-1.2917920	0.1964292
NEUROinvnot neuro-psychiatric	8.3828231	2.0157189	4.1587263	0.0000320
logtime:NEUROinvnot neuro-psychiatric	0.3373798	0.4180306	0.8070697	0.4196263

Table 20: Model with random intercept and slope (noint), including squared log(time).

	Estimate	Std. Error	z value	Pr(> z)
logtime	1.3273264	0.6457149	2.0555920	0.0398219
logtimesquared	-0.3067081	0.2374284	-1.2917920	0.1964292
NEUROinvneuro-psychiatric	13.2004775	1.6672767	7.9173888	0.0000000
NEUROinvnot neuro-psychiatric	21.5833006	1.1498601	18.7703717	0.0000000
logtime:NEUROinvnot neuro-psychiatric	0.3373798	0.4180306	0.8070697	0.4196263

Table 21: Model with random intercept and slope (noint), including squared log(time).

	Estimate	Std. Error	z value	Pr(> z)
logtime	1.3273264	0.6457149	2.0555920	0.0398219
logtimesquared	-0.3067081	0.2374284	-1.2917920	0.1964292
NEUROinvneuro-psychiatric	13.2004775	1.6672767	7.9173888	0.0000000
NEUROinvnot neuro-psychiatric	21.5833006	1.1498601	18.7703717	0.0000000
logtime:NEUROinvnot neuro-psychiatric	0.3373798	0.4180306	0.8070697	0.4196263

Table 22: Model with random intercept and slope, including squared log(time), age, housing.

	Estimate	Std. Error	z value	Pr(> z)
logtimesquared	-0.3138568	0.2563590	-1.2242864	0.2208442
NEUROinvneuro-psychiatric	17.4688644	2.3923640	7.3019258	0.0000000
NEUROinvnot neuro-psychiatric	23.0627714	2.6165710	8.8141202	0.0000000
age65	-0.4034175	0.1026061	-3.9317120	0.0000843
housinginvalone	5.2544884	2.0433790	2.5714703	0.0101268
housinginvwith family or partner	3.7058294	2.0343071	1.8216667	0.0685056
NEUROinvneuro-psychiatric:logtime	1.1358596	0.7963469	1.4263376	0.1537709
NEUROinvnot neuro-psychiatric:logtime	1.3524008	0.7341295	1.8421828	0.0654484
age65:logtime	0.0171623	0.0254898	0.6732998	0.5007566

Table 23: Model with random intercept and slope, including squared log(time), age, housing.

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	22.7233528	2.2804958	9.9642159	0.0000000
logtime	1.1358596	0.7963469	1.4263376	0.1537709
logtimesquared	-0.3138568	0.2563590	-1.2242864	0.2208442
NEUROinvnot neuro-psychiatric	5.5939070	1.8633798	3.0020219	0.0026819
age65	-0.4034175	0.1026061	-3.9317120	0.0000843
housingwith family or partner	-1.5486590	1.6379606	-0.9454800	0.3444139
housingnursing home	-5.2544884	2.0433790	-2.5714703	0.0101268
logtime:NEUROinvnot neuro-psychiatric	0.2165412	0.4523231	0.4787313	0.6321298
logtime:age65	0.0171623	0.0254898	0.6732998	0.5007566

Table 24: Model with random intercept and slope, including squared log(time), age, housing. (p22-23)

	Estimate	Std. Error	z value	Pr(> z)
logtimesquared	-0.3173590	0.2572524	-1.2336483	0.2173340
NEUROinvneuro-psychiatric	16.9839563	2.5312577	6.7096906	0.0000000
NEUROinvnot neuro-psychiatric	22.3611492	2.8891077	7.7398117	0.0000000
age65	-0.3945235	0.1050362	-3.7560718	0.0001726
housinginvalone	6.3369899	2.3500178	2.6965710	0.0070057
housinginvwith family or partner	4.0939949	2.3592488	1.7352960	0.0826884
NEUROinvneuro-psychiatric:logtime	1.3951547	0.9112332	1.5310623	0.1257540
NEUROinvnot neuro-psychiatric:logtime	1.7357817	1.0014381	1.7332892	0.0830443
age65:logtime	0.0119440	0.0278845	0.4283380	0.6684051
housinginvalone:logtime	-0.5574632	0.6218800	-0.8964161	0.3700305
housinginvwith family or partner:logtime	-0.2094627	0.6333212	-0.3307369	0.7408432

Table 25: Model with random intercept and slope, including squared log(time), age, housing. (p26)

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	16.9839563	2.5312577	6.7096906	0.0000000
logtime	1.3951547	0.9112332	1.5310623	0.1257540
logtimesquared	-0.3173590	0.2572524	-1.2336483	0.2173340
NEUROinvnot neuro-psychiatric	5.3771929	1.9151297	2.8077434	0.0049890
age65	-0.3945235	0.1050362	-3.7560718	0.0001726
housinginvalone	6.3369899	2.3500178	2.6965710	0.0070057
housinginvwith family or partner	4.0939949	2.3592488	1.7352960	0.0826884
logtime:NEUROinvnot neuro-psychiatric	0.3406270	0.5198916	0.6551885	0.5123464
logtime:age65	0.0119440	0.0278845	0.4283380	0.6684051
logtime:housinginvalone	-0.5574632	0.6218800	-0.8964161	0.3700305
logtime:housinginvwith family or partner	-0.2094627	0.6333212	-0.3307369	0.7408432

Table 26: Model with random intercept and slope, including age, housing. (p28)

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	16.8550174	2.1870177	7.706850	0.0000000
logtime	0.7939923	0.2019623	3.931389	0.0000845
NEUROinvnot neuro-psychiatric	5.9553777	1.6692342	3.567731	0.0003601
age65	-0.3677716	0.0904074	-4.067937	0.0000474
housinginvalone	5.3051458	2.0469449	2.591738	0.0095492
housinginvwith family or partner	3.8107570	2.0359397	1.871744	0.0612421

4 Conclusion

5 Bibliography