PHP 2516: HW #2

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Question 1: Using the 'calcium_allL' dataset please answer the following questions assuming an unstructured covariance pattern:

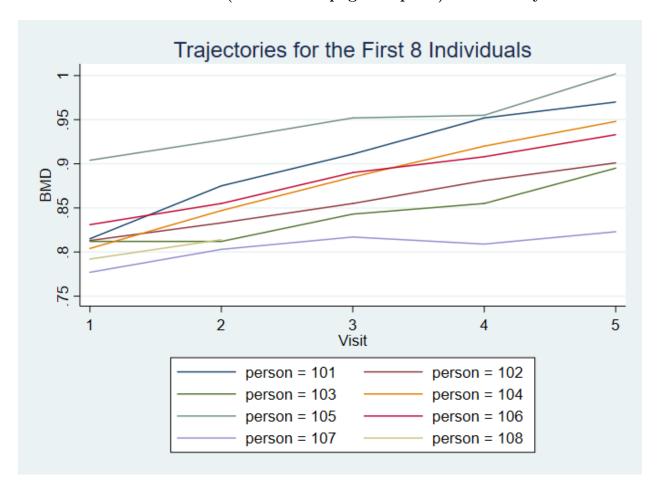
a. Describe the missing patterns you see in the data (if any).

We used the xtdescribe command to show the pattern of missingness in the data:

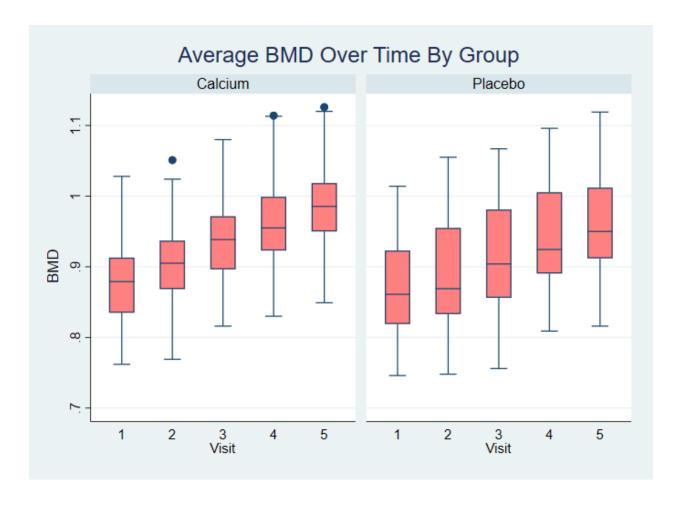
Freq.	Percent	Cum.	Pattern
91	81.25	81.25	11111
7	6.25	87.50	1
6	5.36	92.86	11
5	4.46	97.32	111
3	2.68	100.00	1111.
112	100.00		xxxxx

We see from the table above that 91 people had all five observations, 7 people had only the first observation, 6 people had only the first and second observation, and etc. It appears that people that drop out of the study do not return at a later time.

b. Plot the observed data (means and spaghetti plots). What do you observe?



The spaghetti plot above shows the trajectories for the first 8 individuals. We see that there appears to be an upward trend of bone mineral density over time.



The boxplots also display an upward trend in bone mineral density. Visually, the calcium group and control group seem to have the same rate of increase. The overall means in the calcium group appear to be higher than the means in the placebo group.

c. Conduct a Mean Response Profiles analysis (Model 1) with only time and treatment group. What is your overall conclusion about the changes in the mean response over time and the effect of the treatment group on those changes?

The mean response profile uses all variables as categorical and takes the form:

$$(1): BMD_i = \beta_0 + \sum_{n=1}^4 \beta_n visit + \beta_5 tx + \sum_{m=6}^{10} \beta_m visit * tx + \epsilon_i$$

The regression result from model (1) is:

bmd	Coef.	Std. Err.	Z	P> z	[95% Conf.	Interval]
visit						
2	.0200641	.0023589	8.51	0.000	.0154408	.0246875
3	.0441663	.0033297	13.26	0.000	.0376402	.0506924
4	.0705428	.0039355	17.92	0.000	.0628294	.0782563
5	.0870585	.0043331	20.09	0.000	.0785657	.0955513
tx						
Treatment	.0103844	.011881	0.87	0.382	012902	.0336707
visit#tx						
2#Treatment	.0069691	.0033527	2.08	0.038	.000398	.0135402
3#Treatment	.0123047	.0047558	2.59	0.010	.0029836	.0216259
4#Treatment	.0124964	.0056195	2.22	0.026	.0014824	.0235103
5#Treatment	.0189692	.0061952	3.06	0.002	.0068268	.0311115
_cons	.8700702	.0083258	104.50	0.000	.8537519	.8863884

The regression coefficients are interpreted in detail in Question 4.

d. Suppose that you are mainly interested in describing the trends in the mean responses over time adjusting for age. Find a model for the mean that best fits your data.

We start the model selection process with a full marginal model (using time as a continuous predictor) (model2):

$$(2): BMD_i = \beta_0 + \beta_1 visit + \beta_2 visit^2 + \beta_3 tx + \beta_4 age + \beta_5 tx * visit + \beta_6 tx * visit^2 + \beta_7 tx * age + \epsilon_6 tx * visit^2 + \beta_7 tx * age + \epsilon_7 t$$

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0017705	.0096601	0.18	0.855	017163	.0207041
visit2	0001578	.0005065	-0.31	0.755	0011505	
t x	.0951248	.2652323	0.36	0.720	424721	.6149706
age	.0431855	.0183667	2.35	0.019	.0071875	.0791835
txvisit txvisit2	.0117916 0005234	.0133344	0.88 -0.72	0.377	0143433 001942	.0379265
txage	0084595	.0251906	-0.34	0.737	0578321	.0409131
_cons	.3900983	.1933508	2.02		.0111378	.7690589

We see that no predictors are statistically significant in this full model. We then run the model without the interaction between treatment and visit² (dropped because of complexity):

$$(3): BMD_i = \beta_0 + \beta_1 visit + \beta_2 visit^2 + \beta_3 tx + \beta_4 age + \beta_5 tx * visit + \beta_6 tx * age + \epsilon$$

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0035449	.0094089	0.38	0.706	0148963	.021986
visit2	0004217	.0003609	-1.17	0.243	001129	.0002856
tx	.0938985	.2650567	0.35	0.723	425603	.6134
age	.0429718	.0183593	2.34	0.019	.0069883	.0789553
txvisit	.008424	.0125525	0.67	0.502	0161785	.0330265
txage	0083415	.0251736	-0.33	0.740	0576809	.0409979
_cons	.3923219	.1932742	2.03	0.042	.0135114	.7711323

Again, there are no statistically significant predictors. We decide again to drop the more complicated term, visit², and rerun the regression (model4):

$$(4): BMD_i = \beta_0 + \beta_1 visit + \beta_2 tx + \beta_3 age + \beta_4 tx * visit + \beta_5 tx * age + \epsilon$$

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0008886	.0091447	0.10	0.923	0170346	.0188119
tx	.0951723	.2654472	0.36	0.720	4250945	.6154392
age	.0429505	.0183775	2.34	0.019	.0069312	.0789698
txvisit	.0084772	.0125714	0.67	0.500	0161623	.0331167
txage	0084588	.0252109	-0.34	0.737	0578713	.0409537
_cons	.3925635	.193466	2.03	0.042	.0133772	.7717499

We see again that non of the predictors are significant at the .05 level. We then decide to drop the least significant interaction term (tx*age) (model5):

$$(5): BMD_i = \beta_0 + \beta_1 visit + \beta_2 tx + \beta_3 age + \beta_4 tx * visit + \epsilon$$

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0031635	.0062964	0.50	0.615	0091772	.0155041
tx	.0062377	.0112506	0.55	0.579	0158131	.0282884
age	.0383463	.0125607	3.05	0.002	.0137278	.0629648
txvisit	.0042865	.0014821	2.89	0.004	.0013815	.0071914
_cons	.4409402	.1323538	3.33	0.001	.1815314	.7003489

In model 5, we see that the interaction between treatment and visit is significant as well as the coefficient on age. Since interaction terms lose their interpretability when the individual predictors of the interaction are

dropped, we elect to keep visit and treatment in the model, despite the lack of significance. We thus choose model 5 as our best model.

We also check the information criteria for all 5 models:

Model	Obs	11 (null)	11 (model)	df	AIC	BIC
modell	501		1173.17	25	-2296.34	-2190.925
model2	501		1181.694	23	-2317.388	-2220.406
model3	501		1187.751	22	-2331.502	-2238.737
model4	501		1194.156	21	-2346.313	-2257.764
model5	501		1196.864	20	-2353.728	-2269.396

As expected we see that model 5 has the lowest AIC and BIC.

Question 2: : Using the best model from q1 part d try the following covariance patterns:

We rerun our model 5 using seven different covariance structures. Here is the regression output for each:

a. Unstructured

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit tx age txvisit	.0031635 .0062377 .0383463	.0062964 .0112506 .0125607	0.50 0.55 3.05 2.89	0.615 0.579 0.002 0.004	0091772 0158131 .0137278	.0155041 .0282884 .0629648
_cons	.4409402	.1323538	3.33	0.004	.1815314	.7003489

b. Exchangable

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	0052147	.0073783	-0.71	0.480	0196759	.0092465
tx	.0072468	.0130863	0.55	0.580	0184019	.0328955
age	.0564111	.0148839	3.79	0.000	.0272392	.0855829
txvisit	.0044043	.0009836	4.48	0.000	.0024765	.0063321
_cons	.2503899	.1576196	1.59	0.112	0585387	.5593186

c. Autoregressive (1)

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.007089	.0064485	1.10	0.272	0055498	.0197278
tx	.0057492	.0130241	0.44	0.659	0197774	.0312759
age	.0296696	.0128456	2.31	0.021	.0044926	.0548466
txvisit	.0047171	.0015962	2.96	0.003	.0015886	.0078456
_cons	.5348164	.1360546	3.93	0.000	.2681543	.8014786

d. Autoregressive (3)

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0068361	.0064825	1.05	0.292	0058694	.0195416
tx	.0058168	.0130241	0.45	0.655	0197099	.0313435
age	.0302843	.0129249	2.34	0.019	.0049519	.0556166
txvisit	.0047016	.0015644	3.01	0.003	.0016353	.0077678
_cons	.5282109	.1368967	3.86	0.000	.2598983	.7965234

e. Toeplitz (1)

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0138843	.0104262	1.33	0.183	0065506	.0343192
tx	.0067486	.0129569	0.52	0.602	0186464	.0321435
age	.0161105	.0203566	0.79	0.429	0237877	.0560087
txvisit	.0048153	.0039542	1.22	0.223	0029348	.0125654
_cons	. 6778402	.2145347	3.16	0.002	.25736	1.09832

f. Toeplitz (3)

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0072544	.0073514	0.99	0.324	0071539	.0216628
tx	.0024347	.0136204	0.18	0.858	0242608	.0291303
age	.0250645	.0136917	1.83	0.067	0017706	.0518997
txvisit	.0054828	.0039831	1.38	0.169	0023238	.0132895
_cons	.5882832	.1447269	4.06	0.000	.3046237	.8719427

g. Toeplitz (4)

bmd	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
visit	.0072544	.0073514	0.99	0.324	0071539	.0216628
tx	.0024347	.0136204	0.18	0.858	0242608	.0291303
age	.0250645	.0136917	1.83	0.067	0017706	.0518997
txvisit	.0054828	.0039831	1.38	0.169	0023238	.0132895
_cons	.5882832	.1447269	4.06	0.000	.3046237	.8719427

To choose the best fit from the seven different covariance structures, we examine the information criteria:

Model	Obs	11 (null)	11 (model)	df	AIC	BIC
unstr	501		1196.864	20	-2353.728	-2269.396
exch	501		1121.253	7	-2228.506	-2198.99
autol	501		1180.889	7	-2347.777	-2318.261
auto3	501		1180.966	9	-2343.931	-2305.982
toel	501		852.9992	7	-1691.998	-1662.482
toe3	501		1078.897	9	-2139.795	-2101.845
toe4	501		1078.897	9	-2139.795	-2101.845

Because it has the lowest BIC, we believe that the model with a 1 period autoregressive covariance structure is the best fit.

Question 3: Start with a simple model assuming only a linear trend over time, the main effect of treatment, no interaction between time and treatment, and no adjustment for other covariates.

a,b,c. Select the model that best fits the covariance in your data among the seven options given in question 2. Then fit the model that best describes the trends in the mean responses over time. Is the final "best" model for your data the same with the one resulted from the process followed in Question 2?

The simplified model is:

$$BMD_i = \beta_0 + \beta_1 visit + \beta_2 tx + \epsilon$$

Using the simplified model, we run the regression with the seven different covariance structures from question 2 and examine the information criteria for each regression:

Obs	ll(null)	11(model)	df	AIC	BIC
501		1197.707	18	-2359.413	-2283.514
501		1113.933	5	-2217.865	-2196.782
501		1182.795	5	-2355.59	-2334.507
501		1182.822	7	-2351.644	-2322.128
501		859.5332	5	-1709.066	-1687.983
501		1084.229	7	-2154.458	-2124.941
501		1084.229	7	-2154.458	-2124.941
	501 501 501 501 501 501	501 . 501 . 501 . 501 . 501 .	501 . 1197.707 501 . 1113.933 501 . 1182.795 501 . 1182.822 501 . 859.5332 501 . 1084.229	501 . 1197.707 18 501 . 1113.933 5 501 . 1182.795 5 501 . 1182.822 7 501 . 859.5332 5 501 . 1084.229 7	501 . 1197.707 18 -2359.413 501 . 1113.933 5 -2217.865 501 . 1182.795 5 -2355.59 501 . 1182.822 7 -2351.644 501 . 859.5332 5 -1709.066 501 . 1084.229 7 -2154.458

Again, the model with a 1 period autoregressive covariance structure is the best model, in terms of BIC. Because this matches the conclusion in question 2, this may be evidence that the best covariance structure remains constant despite different predictor choices for nested models, although this point may be coincidence and warrants further investigation.

Question 4: Interpret the regression coefficients from Model 1 and the best model(s) for the mean resulted from Q1.d and Q3. What is your final conclusion about the changes in the response over time between the two treatment groups?

Interpretation for our mean response model (model 1):

For model 1, the constant, .87, is the mean BMD for the control group at the first visit.

The beta coefficients for visit are the average increase BMD measurements for the placebo group in reference to the first visit. For example, the average BMD was $.04 \text{ g/cm}^2$ higher on visit three for the placebo group compared to their first visit.

The coefficient on treatment is the average difference in BMD between the calcium and placebo group at the first visit (not significant).

The interaction coefficients represent the average difference between the calcium group and the placebo group at each of the follow up visits. For example, the average BMD measurement was $.012 \text{ g/cm}^2$ higher for the calcium group at visit 4 than the placebo group.

Interpretation for our best marginal model from Q1 (model 5):

Since the data was not centered, the intercept, .44, represents the mean BMD for a 0 year old person in the placebo group.

The coefficient on visit means that the BMD for each additional visit increased by .003 on average for the placebo group.

The coefficient on treatment means that the average BMD for the treatment group at time zero was .006 g/cm² higher than the average in the placebo group (not significant).

The coefficient on age means that for a 1 year increase in age, we expect a .038 increase in BMD measurement on average.

The coefficient on the interaction means that the average marginal increase in BMD is .004 g/cm² higher for the calcium group compared to the placebo group.

Interpretation for our best marginal model from Q3:

The intercept, .841, is the average BMD for visit 1 in the placebo group.

The coefficient on visit means that for each additional visit, we expect the BMD level to be .024 g/cm² higher.

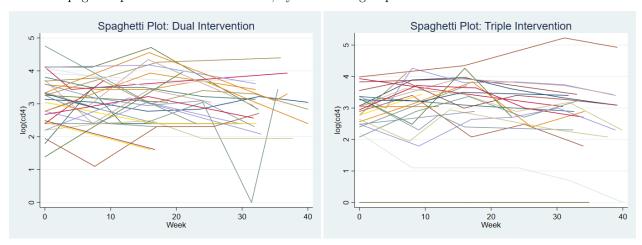
The coefficient on treatment means that we expect the BMD measurement to be .012 g/cm² higher for those in the calcium group compared to the placebo group, all else equal.

After reviewing the model results, it is clear that the mean BMD measurements are increasing over time for both the calcium group and the control group. Because the interaction is significant in model (5), there is evidence to suggest that the rate of increase in BMD is higher for those taking calcium compared to placebo.

Question 5: Using the 'cd4' dataset please answer the following questions:

a. Create spaghetti plots to explore the patterns of the individual trajectories over time, by treatment group. What do you observe?

Here are spaghetti plots for a few individuals, by treatment group:



We observe that in both the dual intervention group and the triple intervention group, the individual trajectories vary greatly. Visually, it is difficult to identify a trend.

b. Based on the plots of the observed data what model would you prefer to fit to express the changes in the primary outcome (log of CD4 counts) over time and any differences between the two treatment groups? Explain.

Because there is a lot of variation in initial log CD4 levels and individual trends over time, we may prefer a mixed effects model that allows for each individual to have their own intercept and slope.

Question 6: Fit a marginal model to describe the trends in the mean responses over time by treatment group. For the mean model consider only a linear trend, and test whether the changes over time are different among the treatment groups without adjusting for any other covariates in the model. For the covariance pattern assume:

To run these regressions, we changed the week variable into an integer variable (intweek) by rounding all the weeks up.

a. Exchangeable

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
trt	.0193174	.0642195	0.30	0.764	1065505	.1451852
intweek	0131325	.0008496	-15.46	0.000	0147977	0114673
trtintweek	.0119722	.0016608	7.21	0.000	.0087171	.0152273
_cons	2.992349	.03231	92.61	0.000	2.929022	3.055675

b. Unstructured

There were too many parameters to estimate for the unstructured covariance matrix.

c. Auto-regressive (1)

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
trt intweek	0467184 01113	.0663259	-0.70 -8.17	0.481	1767149 0137984	.083278
trtintweek	.0141925	.0026772	5.30	0.000	.0089453	.0194397
_cons	2.958933	.03337	88.67	0.000	2.893529	3.024337

d. Toeplitz(1)

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
trt intweek trtintweek _cons	.0153594	.0549684	0.28	0.780	0923766	.1230954
	0105528	.0013807	-7.64	0.000	0132589	0078467
	.0116561	.0027064	4.31	0.000	.0063517	.0169606
	2.985846	.0277626	107.55	0.000	2.931432	3.040259

What do you observe? Do you think that a marginal model is appropriate for analyzing these data? Explain

The three models that run have statistically significant positive interactions between triple intervention and time, meaning that the marginal increase in log CD4 levels is higher for the triple intervention group than the dual intervention group. Although the conclusion is consistent among all the marginal models, a mixed model may be more appropriate to fit. We see in the spaghetti plots above that many individuals have a negative slope in the treatment group. If we are interested in predictions at the individual level, a mixed model that accounts for individual level characteristics would be a better choice.

Question 7: Fit four different models for the covariance in the data, only assuming the following:

a. A random intercept (model1)

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
week	0045968	.0027167	-1.69	0.091	0099213	.0007278
week2	0002531	.0000756	-3.35	0.001	0004013	0001049
trt	. 423783	.3108695	1.36	0.173	18551	1.033076
age	.0121742	.0036784	3.31	0.001	.0049647	.0193838
gender	0019041	.0920833	-0.02	0.984	1823842	.1785759
weektrt	.0371581	.0053368	6.96	0.000	.0266982	.0476181
week2trt	0007291	.0001475	-4.94	0.000	0010182	0004399
agetrt	0035082	.0072268	-0.49	0.627	0176725	.010656
gendertrt	417861	.181678	-2.30	0.021	7739433	0617787
_cons	2.50258	.1559242	16.05	0.000	2.196974	2.808186

b. Random intercept and random slope for time t (model2)

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
week	0037738	.0026288	-1.44	0.151	0089262	.0013785
week2	0002972	.0000727	-4.09	0.000	0004397	0001546
trt	.3630766	.3025003	1.20	0.230	2298132	.9559664
age	.0115266	.00358	3.22	0.001	.0045098	.0185433
gender	.0093256	.0895165	0.10	0.917	1661236	.1847748
weektrt	.037052	.0051613	7.18	0.000	.026936	.047168
week2trt	0007078	.0001418	-4.99	0.000	0009857	0004299
agetrt	0028666	.0070498	-0.41	0.684	016684	.0109508
gendertrt	3779569	.1766732	-2.14	0.032	72423	0316838
_cons	2.5154	.1515171	16.60	0.000	2.218432	2.812368

c. Random intercept and random slopes for time t, and t^2 (model3)

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
week week2 trt age gender weektrt week2trt agetrt	0037738 0002972 .3630764 .0115266 .0093256 .037052 0007078 0028666	.0026288 .0000727 .3025003 .00358 .0895165 .0051613 .0001418	-1.44 -4.09 1.20 3.22 0.10 7.18 -4.99 -0.41	0.151 0.000 0.230 0.001 0.917 0.000 0.000	0089262 0004397 2298132 .0045098 1661235 .026936 0009857 016684	.0013785 0001546 .9559661 .0185433 .1847748 .047168 0004299
gendertrt cons	3779568 2.5154	.1766732 .1515171	-2.14 16.60	0.032	7242298 2.218432	0316837 2.812368
_						

d. random intercept and random slopes for time t, t^2 and age (model4)

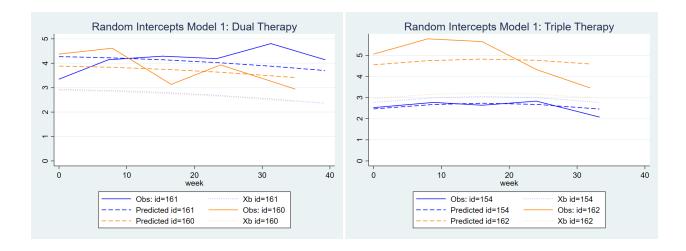
logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
week week2	0037738 0002972	.0026288	-1.44 -4.09	0.151 0.000	0089262 0004397	.0013785 0001546
trt	.3630767	.3025005	1.20	0.230	2298135	. 9559669
age gender	.0115266	.00358 .0895166	3.22 0.10	0.001 0.917	.0045098 1661237	.0185433
weektrt	.037052	.0051613	7.18	0.000	.026936	.047168
week2trt	0007078	.0001418	-4.99	0.000	0009857	0004299
agetrt gendertrt	0028666 3779569	.0070499	-0.41 -2.14	0.684	0166841 7242302	.0109509
_cons	2.5154	.1515172	16.60	0.000	2.218432	2.812368

e. Can you assume a random slope for gender? Explain.

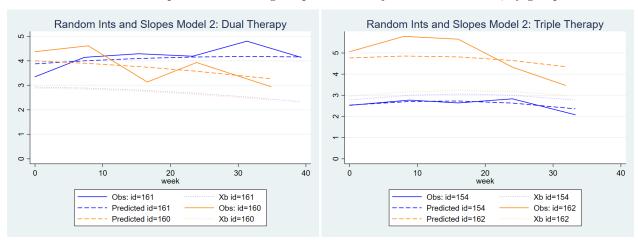
You can not assume a random slope for gender because gender is constant at all time points. Only time varying covariates can be included in the random part of the model.

f. Plot the observed trajectories of four randomly selected individuals; two from the dual and two from the triple therapy. Compare these observed trajectories with the respective model predictions and the linear model mean estimates from each of the four previous models.

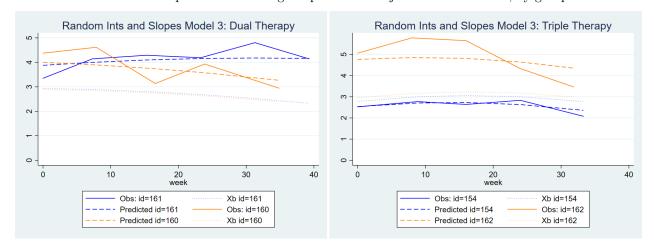
Here are the observed vs individual prediction vs marginal prediction trajectories for model 1, by group:



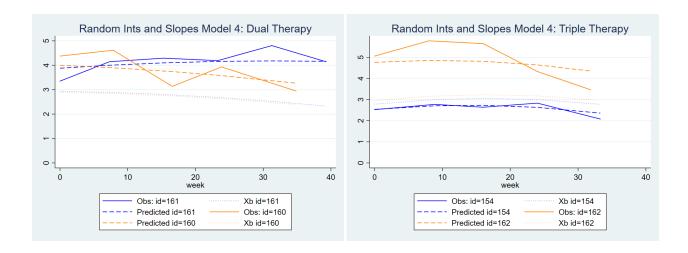
The observed vs individual prediction vs marginal prediction trajectories for model 2, by group:



The observed vs individual prediction vs marginal prediction trajectories for model 3, by group:



Lastly, the observed vs individual prediction vs marginal prediction trajectories for model 4, by group:



In all instances, the mixed effects models predictions are closer to the observed predictions for the individual than the marginal model. We also see that including a random slope seems to improve the fit. Among the models with random slopes, it is difficult to determine visually which fits better (they look similar). The plots for the models with random slopes look similar because most of the variation is captured by the random intercepts. For example, here are the random parameters for model 4:

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
id: Independent				
var(week)	.0003098			
var(week2)	2.90e-23			
var(age)	1.06e-14			
var(_cons)	.6809629			
var(Residual)	.3238026			

We see that the variance absorbed by the constant is .681, which is much larger than the variance in the slope terms.

g. Which of the four models best fits the data? Explain.

We also examine the information criteria for each of the four models:

Model	Obs	11 (null)	11(model)	df	AIC	BIC
randint	5,036		-6092.666	12	12209.33	12287.62
randl	5,036		-6022.316	13	12070.63	12155.45
rand2	5,036		-6022.316	14	12072.63	12163.97
rand3	5,036		-6022.316	10	12064.63	12129.88

The more complex model, which includes a random intercept and random slopes on time, time², and age has the lowest BIC and AIC. We thus believe that this model is best.

Question 8: Based on the best model from the previous question what is your overall conclusion about the effect of the two treatments on the change of the log(CD4) over time?

To recap, here are the results of our best model (model 4):

logcd4	Coef.	Std. Err.	z	P> z	[95% Conf.	Interval]
week	0037738	.0026288	-1.44	0.151	0089262	.0013785
week2	0002972	.0000727	-4.09	0.000	0004397	0001546
trt	.3630767	.3025005	1.20	0.230	2298135	.9559669
age	.0115266	.00358	3.22	0.001	.0045098	.0185433
gender	.0093256	.0895166	0.10	0.917	1661237	.1847749
weektrt	.037052	.0051613	7.18	0.000	.026936	.047168
week2trt	0007078	.0001418	-4.99	0.000	0009857	0004299
agetrt	0028666	.0070499	-0.41	0.684	0166841	.0109509
gendertrt	3779569	.1766733	-2.14	0.032	7242302	0316835
_cons	2.5154	.1515172	16.60	0.000	2.218432	2.812368

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
id: Independent				
var(week)	.0003098			
var(week2)	2.90e-23			
var(age)	1.06e-14			
var(_cons)	.6809629			
var(Residual)	.3238026			

The trend of log CD4 levels over time for the dual intervention group is given by the coefficients on week and week^2. The week coefficient means that log CD4 decreases initially at a rate of .0038. The week^2 coefficient means that the marginal rate of decrease in log CD4 levels is increasing. In other words, the slope starts negative and becomes increasingly more negative over time for the dual intervention group.

The trend of log CD4 levels over time for the triple intervention group is given by the coefficients on week, week x trt, week^2 and week^2 x trt. Initially, the average log CD4 levels are increasing at a rate of .0334 (week + week x trt). The rate of increase is decreasing over time by .001 (week^2 + week^2 x trt). In other words, the slope for the triple intervention group starts positive but becomes less positive, and eventually negative over time.