ANNUAL GROWTH IN PULMONARY FUNCTION IN CHILDREN TREATED WITH INHALED ANTI-INFLAMMATORY DRUGS

Bradley C. Frueh, Holin Chen, Kushagra Vashist, Emily Drzymalla

Emory University

BACKGROUND

Childhood asthma has increased significantly in recent times, with over 7 million children being affected in the U.S (*Controlling Childhood Asthma*, 2018). To promote airflow and relieve acute (potentially life threatening) symptoms, patients are treated with a combination of beta agonists, steroids, and anti-inflammatory. Previous research has shown that treatments such as budesonide (an inhaled glucocorticoid) and nedocromil (an inhaled nonsteroid anti-inflammatory agent) have shown to be beneficial in patients at improving pulmonary function (Bone et al., 1989, O'Connell, 2002).

The Childhood Asthma Management Program (CAMP) Trial is a multicenter, masked, randomized control trial conducted in 1995. The study included children aged 5 to 12 who had mild to moderate asthma, evaluated by screening criteria. Children were randomly assigned to one of three treatment groups: Treatment A (Budesonide), Treatment B (Nedocromil), and Treatment C (placebo). Children's received assigned treatment twice daily for 6 years and had their respiratory function evaluated every two months. At each examination respiratory function was measured twice, once before and once after bronchodilation with assigned treatment. After 6 years treatment was stopped but follow-up continued for 4 more years to investigate the benefits of early intervention.

Our dataset was a teaching dataset provided by the National Heart, Lung and Blood Institute, which contained observations on 2/3^{rds} of subjects from the original CAMP trial with statistical techniques used to anonymize the data. Missing data was rare for FEV1 (0.37% of observations) and nonexistent for all other variables of interest, including: treatment group, baseline age, and gender. Our outcome was post treatment FEV1 and primary exposure was treatment group.

This study aimed to investigate long term differences in the annual rate of growth in pulmonary function as measured by Forced Expiratory Volume Per Second (FEV1). Therefore, our primary research question assessed whether there are differences in annual rate of growth in pulmonary function between children assigned Budesonide, Nedocromil, and placebo. Our secondary research question was is the association in annual rate of growth in pulmonary function and treatment confounded by age or gender i.e., Did the randomization work?

METHODS

Graphical methods were used to assess model assumptions. A multilevel model approach was implemented to model growth in FEV1 measurements over the study period on two levels: individual growth and average growth of the sample. Full Maximum Likelihood and Restricted Maximum Likelihood estimation were used to obtain unbiased parameter estimates, variance components, and goodness of fit statistics. A forward elimination approach was taken to layer variables one by one and the significance of variables was evaluated using likelihood ratio tests on nested models. The final model will only include variables that add to the predictive power of the model or are required to answer the research question. Once an optimal model is determined, error covariance structures will be compared and chosen based on goodness of fit statistics and model parsimony. All statistical modeling was conducted using SAS PROC MIXED using SAS 9.4, and SAS OnDemand for Academics.

RESULTS

Graphical analysis presented evidence that FEV1 measured after bronchodilation changed linearly with time and therefore it was appropriate to model to annual rate of linear growth. The interclass correlation coefficient was 0.404, meaning approximately 40% of the variation in FEV1 measurements was explained by differences in subjects. Post treatment FEV1

was strongly associated with linear time (R_ϵ^2: 0.893) as was expected. Model comparisons concluded there was no confounding by baseline age or gender, meaning randomization was successful. The optimal model regressed post treatment FEV1 on months since randomization and treatment group. The optimal error covariance structure was heterogenous autoregressive. The baseline measurement for the control group was 1.86 (1.79, 1.93) liters of air per second. There was no difference in baseline measurements for FEV1 between treatment groups. The annual growth rate for the control group was 0.23 (0.22, 0.24) liters of air per second per year. There was no difference in growth rates between Treatment A and placebo. There was a significant difference in annual FEV1 growth between Treatment B and placebo. FEV1 grew 8% more annually in Treatment Group B compared to placebo, averaging a change of 0.249 (0.224, 0.273) liters of air per second annually.

Discussion

Evidence suggests there is no difference in annual FEV1 growth between patients who took Budesonide compared to placebo and a slight difference in growth for subjects taking Nedocromil. While unlikely to be observed by chance the difference in growth for Nedocromil is modest and may not be clinically significance. Both age and gender were not significant during model comparisons, confirming potential known and unknown confounders were equally distributed among the treatment groups. Although our results largely confirm results from the original CAMP trial, due to our dataset being a teaching dataset our results are not externally valid. A limitations of the standard multilevel model for change is the large number of assumptions that need to be made, which could lead to invalid estimates of the variance components misleading researchers about the precision of their results.

References

Bone, M. F., Kubik, M. M., Keaney, N. P., Summers, G. D., Connolly, C. K., Burge, P. S., Dent, R. G., & Allan, G. W. (1989). Nedocromil sodium in adults with asthma dependent on inhaled corticosteroids: a double blind, placebo controlled study. *Thorax*, *44*(8), 654–659. https://doi.org/10.1136/thx.44.8.654

Controlling childhood asthma. (2018, March 20). National Institutes of Health (NIH). https://www.nih.gov/news-events/nih-research-matters/controlling-childhood-asthma

O'Connell, E. J. (2002). Efficacy of budesonide in moderate to severe asthma. *Clinical Therapeutics*, *24*(6), 887–905. https://doi.org/10.1016/s0149-2918(02)80005-4

APPENDIX

Group Work:

Holin Chen: Created the profile plots (**Figure 2A, Figure 2B**), converted from long to wide format to get random samples, constructed the flow chart (**Figure 1**) and helped construct the final plot (**Figure 4**).

Kushagra Vashist: Created spaghetti plots by covariate (**Figures 3A1-3C2**), assisted in error covariance testing by creating a correlation matrix of the measurements to assess band symmetry (**Table 6**), and he created a categorical time graph when we were not sure how to present our final results (**Figure 5**)

Emily Drzymalla: She investigated missingness of variable (**Table 5**) , created histograms and scatter plots to assess normality and linearity assumptions, she created our table of baseline characteristics (**Table 1**), and our table of observations per measurement occasion (**Table 2**).

Bradley Frueh: Conducted the model comparisons and created the table with fixed effects, random effects, and pseudo R-square statistics (**Table 3**). Conducted the error covariance testing and created the table of fit statistics (**Table 4**). Assisted in the creation of the final graph and provided the annotations for the slopes and confidence intervals (**Figure 4, Table 7**).

Table 1: Demographic and Baseline Characteristics

		Treatment Group mean(sd) or n(%)			
Variable		Total (n = 695)	Budesonide (n = 210)	Nedocromil (n = 210)	Placebo (n = 275)
Age	Baseline	8.38 (2.16)	8.51 (2.14)	8.30 (2.17)	8.33 (2.17)
Gender	Female	283 (40.72%)	84 (40.00%)	70 (33.33%)	129 (46.91%)
Ethnic	Black White Hispanic Other	89 (12.81%) 479 (68.92%) 68 (9.78%) 59 (8.49%)	27 (9.52%) 142 (67.62%) 20 (9.52%) 21 (10.0%)	27 (12.86%) 143 (63.10%) 23 (10.95%) 17 (8.10%)	35 (12.73%) 194(70.55%) 25 (9.09%) 21 (7.64%)
Hemoglobin (g/dl)	Baseline	13.12 (1.16)	13.11 (1.27)	13.11 (1.29)	13.15 (0.95)
White Blood Count (1000 cells/ul)	Baseline	73.94 (22.62)	73.65 (22.03)	74.76 (23.94)	73.54 (22.09)
Age of current home (years)	Baseline	32.64 (26.12)	32.73 (26.48)	30.55 (26.84)	34.18 (25.27)
At least one pet (Yes)	Baseline	487 (70.07%)	145 (69.05%)	151 (71.90%)	191 (69.45%)
	Baseline (Yes)	59 (8.50%)	11 (5.26%)	22 (10.48%)	26 (9.45%)

Use of a dehumidifier	Baseline (Unknown)	18 (2.59%)	7 (3.35%)	6 (2.86%)	5 (1.82%)
Used a wood stove (Yes)	Baseline	58 (8.36%)	15 (7.14%)	18 (8.61%)	25 (9.09%)
At least one smoking parent at home (Yes)	Baseline	196 (28.20%)	60 (28.57%)	56 (26.67%)	80 (29.09%)
Anyone smokes at home (Yes)	Baseline	209 (30.07%)	65 (30.95%)	59 (28.10%)	85 (30.91%)

Table 2: FEV1 Observations at Each Measurement Occasion

Post FEV Follow-up Measurements (months)	Available observations (n (%))
0	695 (100.00%)
2	664 (95.54%)
4	673 (96.83%)
12	674 (96.98%)
16	666 (95.83%)
24	661 (95.11%)
28	639 (91.94%)
36	651 (93.67%)
40	632 (90.94%)
44	10 (1.42%)
48	629 (90.50%)
52	424 (61.10%)
56	140 (20.14%)
60	454 (65.32%)
64	19 (2.73%)
72	591 (85.04%)
84	577 (83.02%)
96	577 (83.02%)
108	498 (71.65%)
120	73 (10.50%)

Table 3: A Taxonomy of Models

		Parameter	Model A	Model B	Model C	Model D	Model E
Fixed Effects							
Initial Status							
	Intercept	γ_{00}	2.5981***	1.8316***	1.8595***	1.7175***	1.8836***
			(0.024)	(0.023)	(0.037)	(0.097)	(0.043)
	Treatment A	γ_{01}			0.01711~	0.01412~	0.01362~
					(0.056)	(0.056)	(0.056)
	Treatment B	γ_{02}			-0.1093~	-0.1087~	-0.1162*
					(0.056)	(0.056)	(0.056)
	Age at Randomization	γ_{03}				0.01704~	
						(0.011)	
	Gender	γ_{04}					-0.05144~
							(0.047)
Rate of Change							
	Intercept	γ_{10}		0.01964***	0.01913***	0.02078***	0.01903***
				(<0.001)	(<0.000)	(0.001)	(<0.001)
	Treatment A	γ_{11}			0.000101~	0.000139~	0.000113~
					(0.001)	(0.001)	(0.001)
	Treatment B	γ_{12}			0.001598*	0.001587*	0.001626*
					(0.001)	(0.001)	(0.001)
	Age at Randomization	γ_{13}				-0.0020~	.
						(<0.001)	
	Gender	γ_{14}					0.000215~
							(0.001)
Variance Components							
Level 1	**Within-person**	σ_ε^2	0.5273***	0.05661***	0.05660***	0.05660***	0.05661***
			(0.008)	(<0.001)	(<0.001)	(0.001)	(0.001)
Level 2	**Initial Status**	σ_0^2	0.3577***	0.3656***	0.3627***	0.3614***	.0.3621***
			(0.021)	(0.020)	(0.020)	(0.020)	(0.020)
	Rate of Change	σ_1^2		0.000042***	0.000042***	0.000042***	0.000042***
				(<0.001)	(<0.001)	(<0.001)	(<0.001)
	Covariance	σ_{10}^2		-0.00052**	-0.00049**	-0.00047**	-0.00048**
				(<0.001)	(<0.001)	(<0.001)	(<0.001)
Pseudo R-square Statistics and Goodness of Fit							
		$R_{y,\hat{y}}^2$		0.4545	0.4556	0.4559	0.4559
		R_ε^2		0.89	0.89	0.89	0.89
		R_0^2			0.008	0.011	0.010
		R_1^2			<0.001	<0.001	<0.001
	Deviance		23407.3	4430.8	4419.7	4415.2	4418.5
	AIC		23413.3	4442.8	4439.7	4439.2	4442.5
	BIC		23426.9	4470.0	4485.1	4493.7	4497.0

~p >0.05; *p <0.05; **p<0.01; ***p<0.001

Table 4: Error Covariance Structures and Fit Statistics

Descr	IND	STD	UN	CS	CSH	AR	ARH	TOEP
-2 Res Log Likelihood	20915.47	4474.13	No Fit	8250.75	5877.71	-851.687	-2034.63	-1314.30
AIC (Smaller is Better)	20917.47	4482.13	No Fit	8254.75	5919.71	-847.687	-1992.63	-1274.30
AICC (Smaller is Better)	20917.47	4482.14	No Fit	8254.76	5919.80	-847.685	-1992.53	-1274.21
BIC (Smaller is Better)	20922.02	4500.31	No Fit	8263.84	6015.13	-838.599	-1897.21	-1183.42

Table 5: Table of Missingness for Variables of Interest

Missing Data Patterns									
								Group Means	
Group	POSFEV	TG	visitc	age_rz	GENDER	Freq	Percent	POSFEV	age_rz
1	X	X	X	X	X	9910	99.63	2.614742	8.339859
2	.	X	X	X	X	37	0.37	.	8.918919

Tabe 6: Correlation Matrix of Measurement Occasions

Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations					
	Measurement1	Measurement5	Measurement10	Measurement15	Measurement19
Measurement1	1.00000 663	0.93092 <.0001 639	0.86836 <.0001 607	0.77735 <.0001 569	0.49452 <.0001 67
Measurement5	0.93092 <.0001 639	1.00000 661	0.90441 <.0001 620	0.77663 <.0001 578	0.50936 <.0001 70
Measurement10	0.86836 <.0001 607	0.90441 <.0001 620	1.00000 626	0.87803 <.0001 586	0.62129 <.0001 67
Measurement15	0.77735 <.0001 569	0.77663 <.0001 578	0.87803 <.0001 586	1.00000 587	0.79502 <.0001 64
Measurement19	0.49452 <.0001 67	0.50936 <.0001 70	0.62129 <.0001 67	0.79502 <.0001 64	1.00000 71

Table 7: Annotation Dataset Used in Final Plot

function	x1	y1	width	rotate	textsize	transparency	textweight	label
text	75	38	100	0	8	0	bold	Annual Growth in FEV1 by Treatment Group
text	75	35	100	0	8	0	normal	A: 0.231 (Ltr per sec/ per yr) p-value: 0.87
text	75	32	100	0	8	0	normal	B: 0.249 (Ltr per sec/ per yr) p-value: 0.01
text	72.15	29	100	0	8	0	normal	C: 0.230 (Ltr per sec/ per yr) (Ref)

Figure 1: Sample Size Flow Diagram

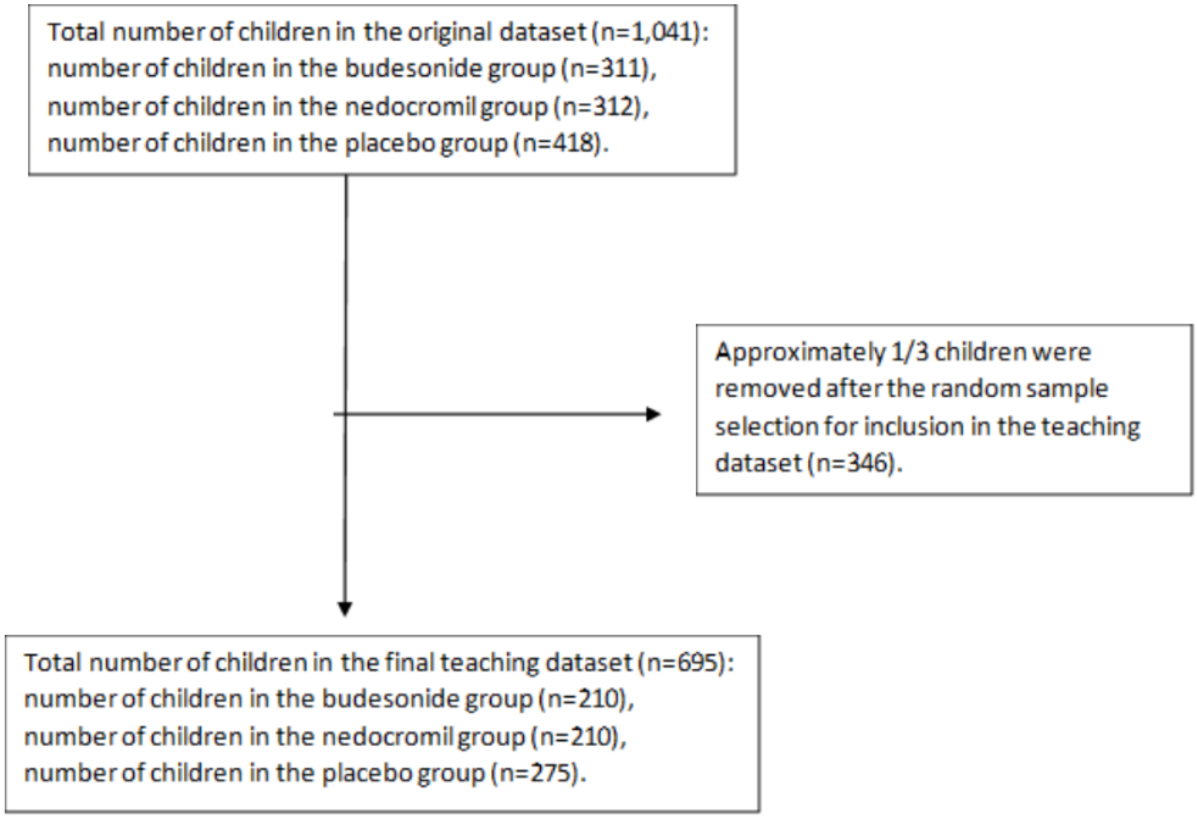


Figure 2A: Profile Plots of Linear Growth in FEV1

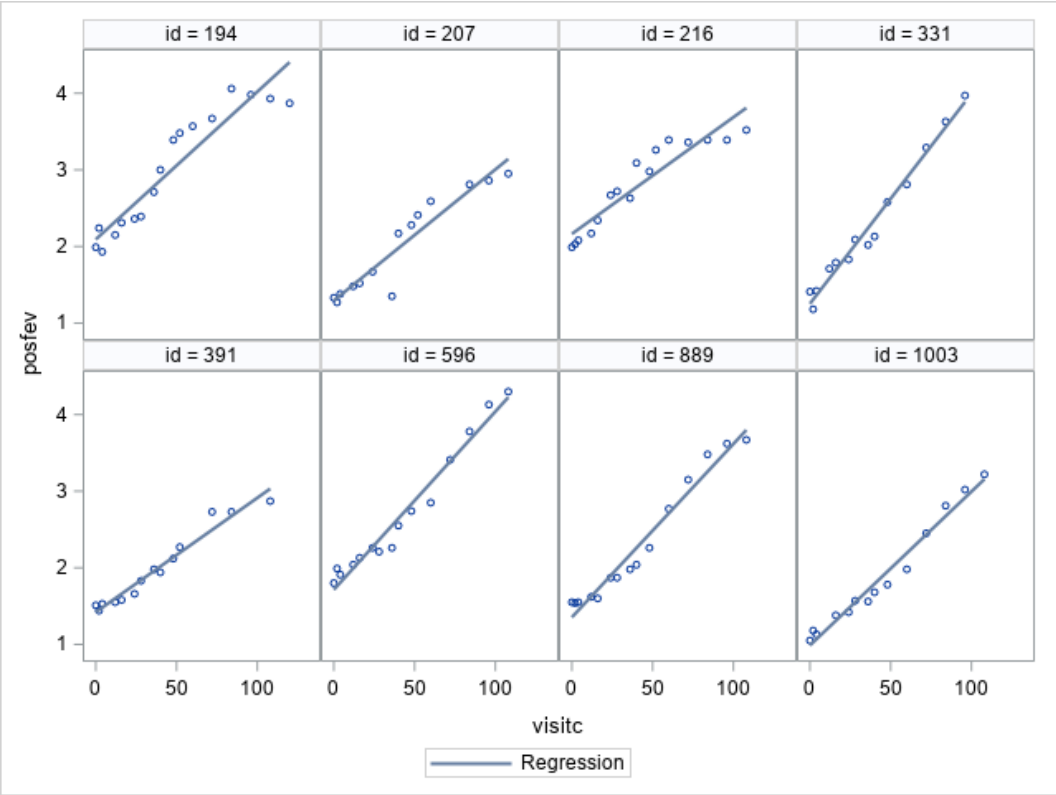


Figure 2B: Profile Plots of Curvilinear

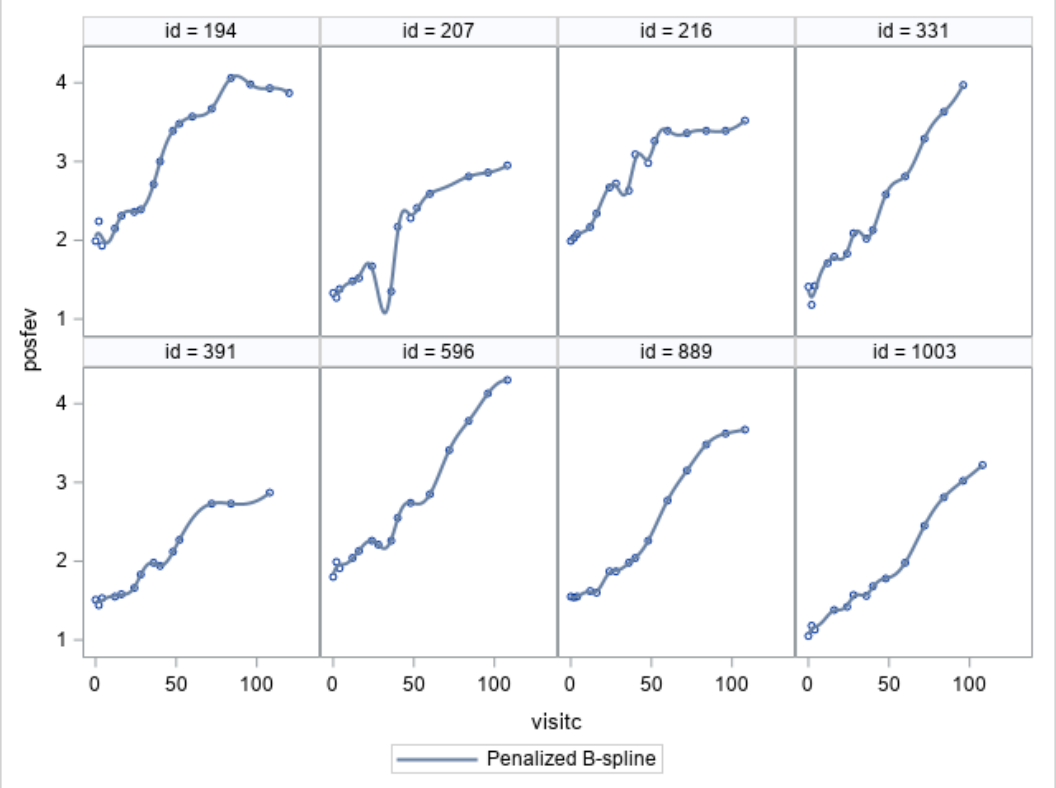


Figure 3A-1: Curvilinear Spaghetti Plots for Treatment Group A (Budesonide)

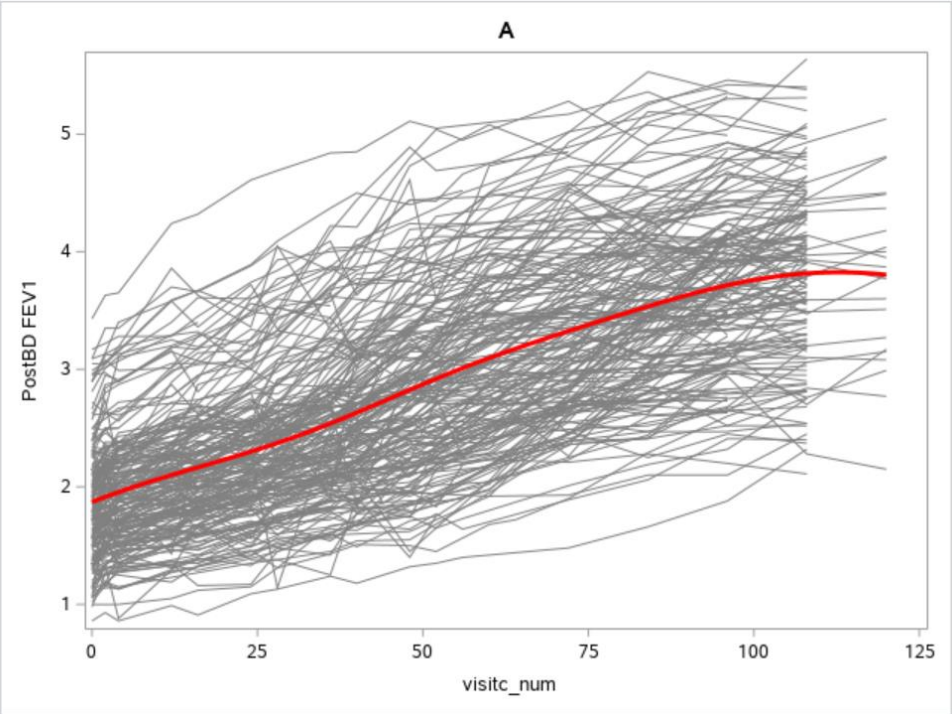


Figure 3A-2: Linear Spaghetti Plots for Treatment Group A (Budesonide)

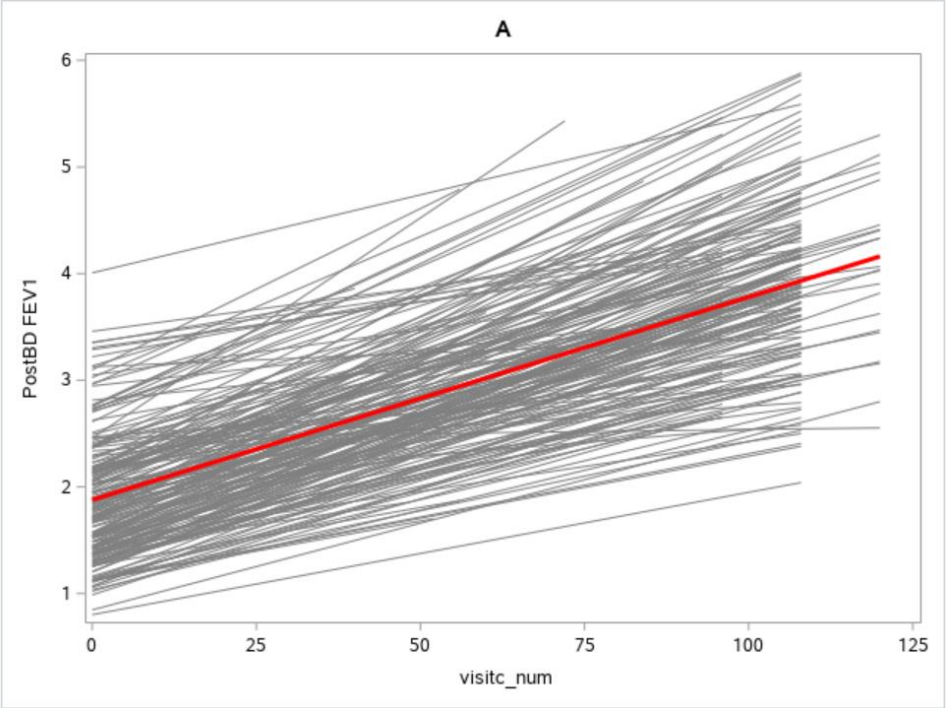


Figure 3B-1: Curvilinear Spaghetti Plots for Treatment Group B (Nedocromil)

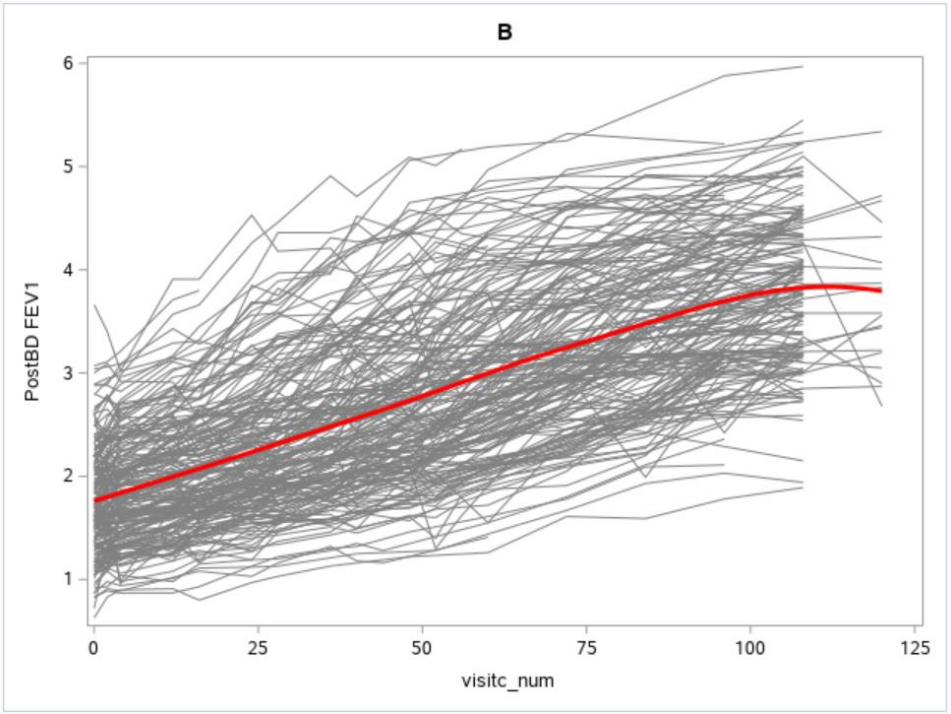


Figure 3B-2: Linear Spaghetti Plots for Treatment Group B (Nedocromil)

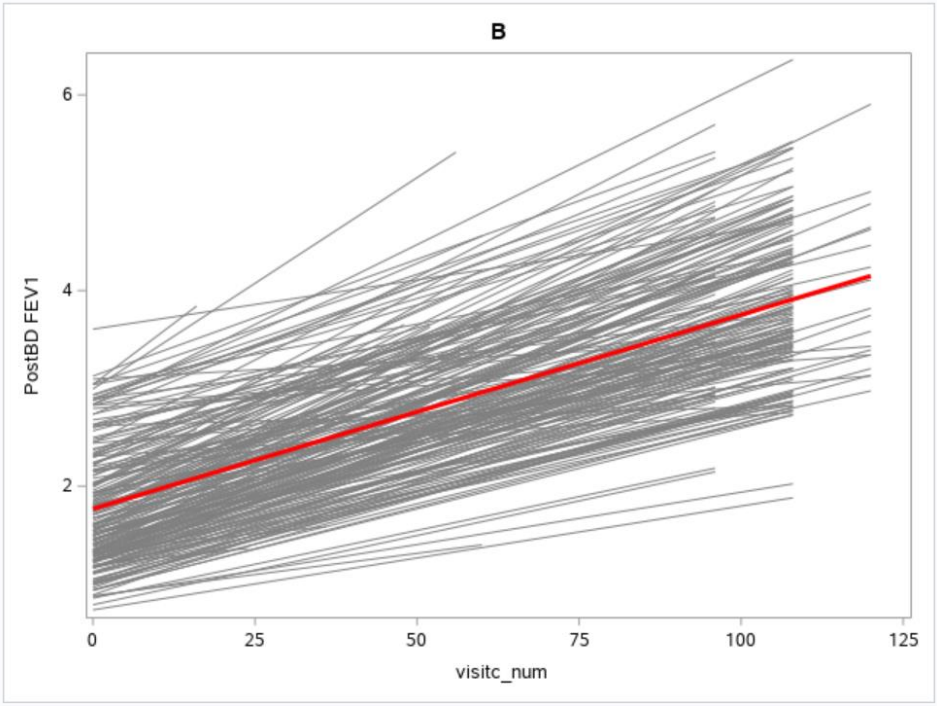


Figure 3C-1: Curvilinear Spaghetti Plots for Treatment Group C (Albuterol)

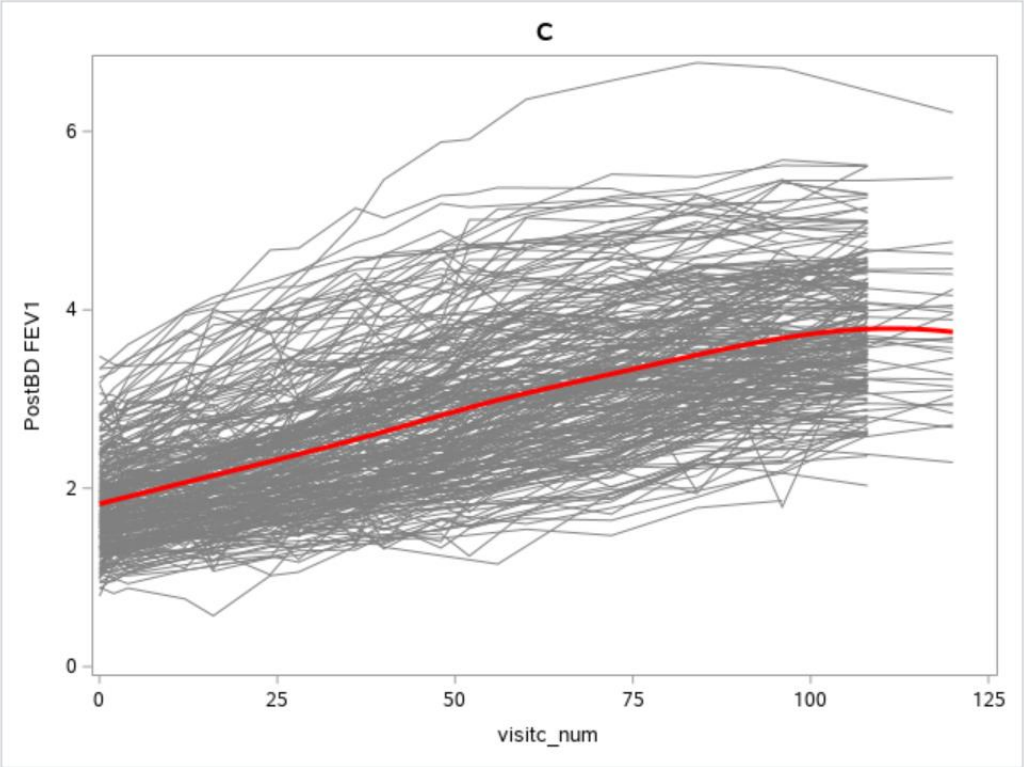


Figure 3C-2: Linear Spaghetti Plots for Treatment Group C (Albuterol)

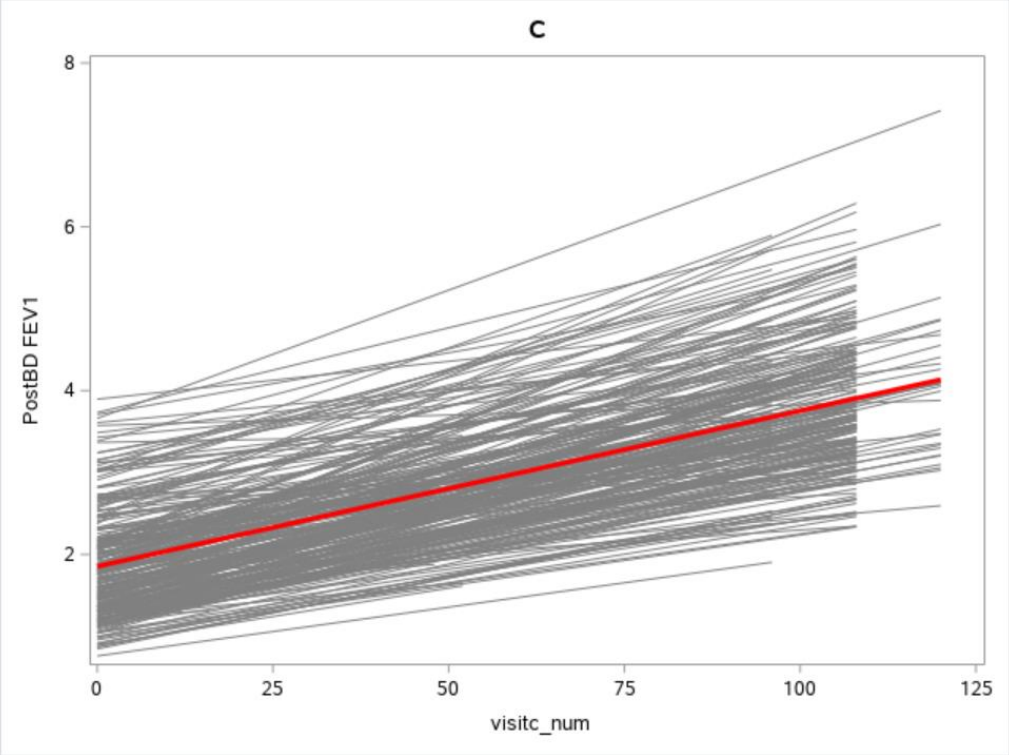


Figure 4: FEV1 Growth Trajectories by Treatment Group

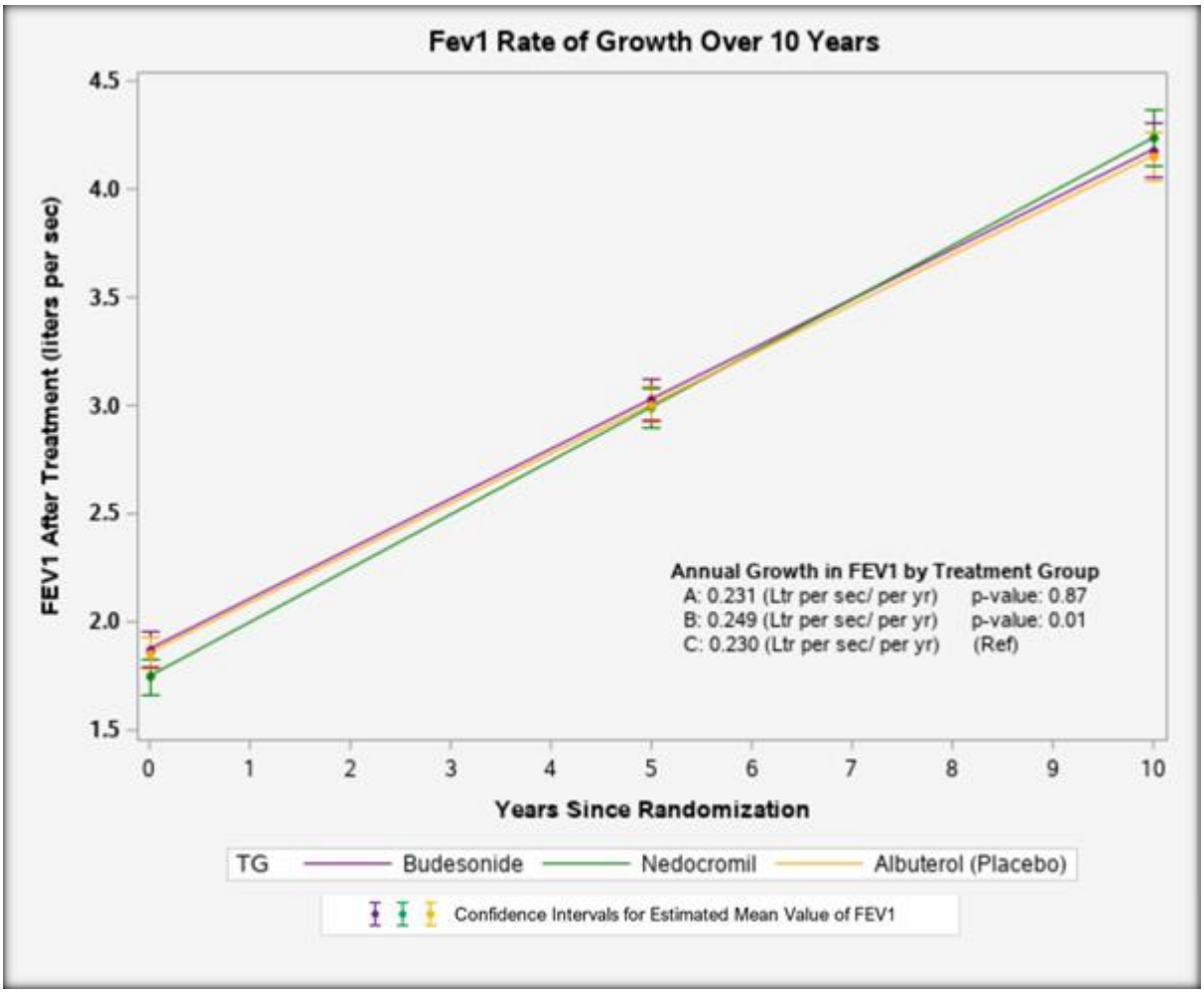
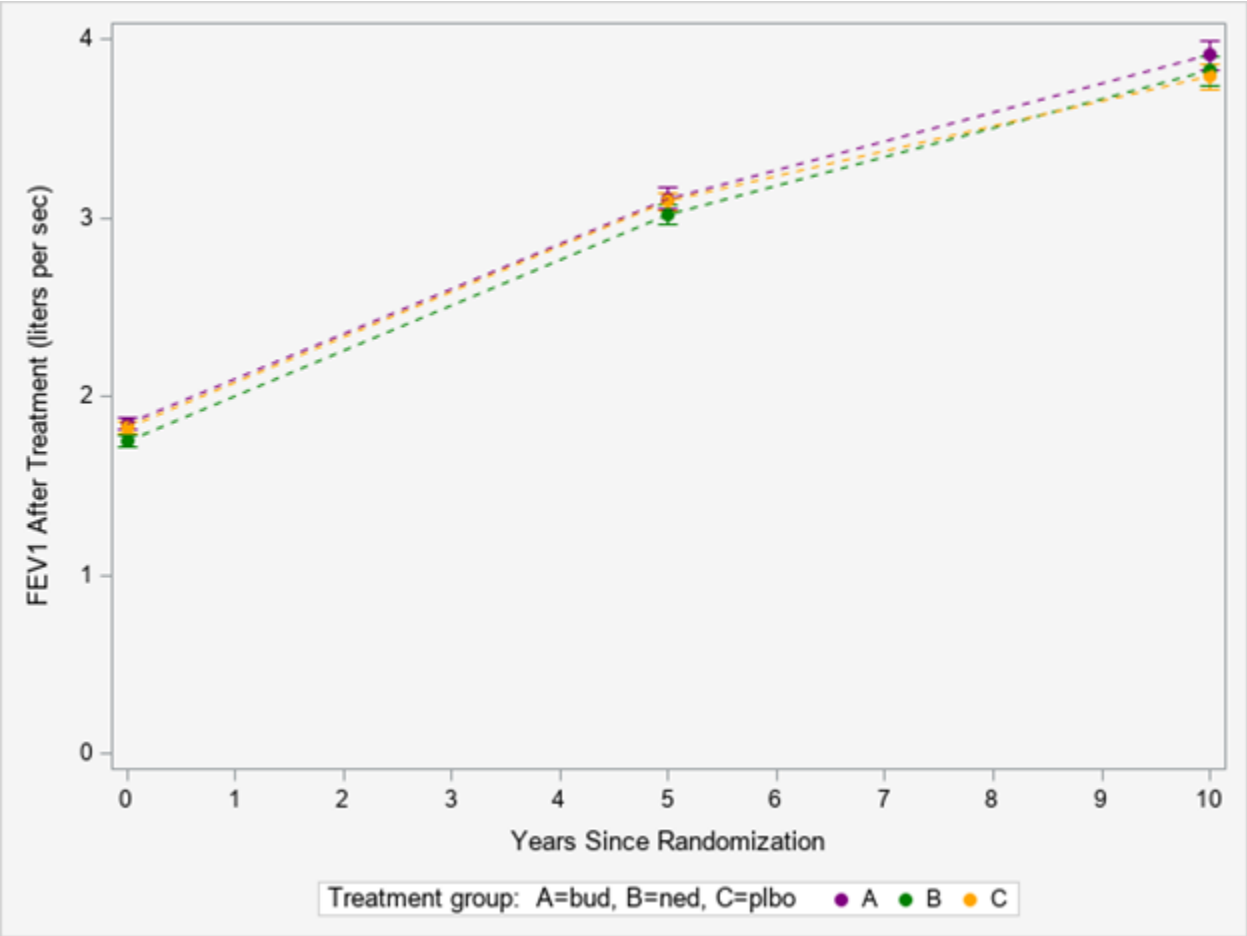


Figure 5: Mean FEV1 by Treatment Group at Baseline, 5 Years and 10 Years



Final Code:

```
libname c "/home/u49993673/CAMP";
proc contents data=c.camp_teach;
run;

*********************************************************************
Create a subset of CAMP_teach with variables of interest
*********************************************************************;

*Change time var to numeric;
Data c.camp;
set c.camp_teach;
if visitc = "000" then visitc_num = 0;
if visitc = "002" then visitc_num = 2;
if visitc = "004" then visitc_num = 4;
if visitc = "012" then visitc_num = 12;
if visitc = "016" then visitc_num = 16;
if visitc = "024" then visitc_num = 24;
if visitc = "028" then visitc_num = 28;
if visitc = "036" then visitc_num = 36;
if visitc = "040" then visitc_num = 40;
if visitc = "044" then visitc_num = 44;
if visitc = "048" then visitc_num = 48;
if visitc = "052" then visitc_num = 52;
if visitc = "056" then visitc_num = 56;
if visitc = "060" then visitc_num = 60;
if visitc = "064" then visitc_num = 64;
if visitc = "072" then visitc_num = 72;
if visitc = "084" then visitc_num = 84;
if visitc = "096" then visitc_num = 96;
if visitc = "108" then visitc_num = 108;
if visitc = "120" then visitc_num = 120;
fup_yr = visitc_num / 12; *<---Create a time variable for years;
waves = visitc_num;
keep posfev gender ethnic gender age_rz TG
visitc id waves visitc_num fup_yr;
run;

*********************************************************************
                Create profile plots for posfev
*********************************************************************;


*Convert from long to Wide Format;
data camp;
set c.camp;
```

```
run;

proc sort data=camp;
by id;
run;

proc transpose data=camp out=camp_wide prefix=posfev_wide;
by id;
id visitc_num;
var posfev;
run;

proc print data=camp_wide (obs=10);
run;

*****************************************************************
* posfev_wide is not in the right order. Variables appear in the order
they were created which is not what we want. *
* Reorder variables using RETAIN statement *
*****************************************************************;


proc contents data=camp_wide varnum;
ods output position = camp_wide_var; *<--- Proc contents has variables
in order;
run;

data camp_wide_var;
set camp_wide_var;
keep variable; *<----Drop useless info to grab variables easier;
run;

proc print data=camp_wide_var noobs;
run; *Copy and paste the single column of variables for
RETAIN               statement;

data camp_wide2;
 retain _label_ _name_ id
posfev_wide0
posfev_wide2
posfev_wide4
posfev_wide12
posfev_wide16
posfev_wide24
posfev_wide28
posfev_wide36
```

```
posfev_wide40
posfev_wide44
posfev_wide48
posfev_wide52
posfev_wide56
posfev_wide60
posfev_wide64
posfev_wide72
posfev_wide84
posfev_wide96
posfev_wide108
posfev_wide120;
set camp_wide;
run;

*Posfev_wide is now in the correct order!;
proc print data=camp_wide2 (obs=10);
run;

*Make it permanent;
data c.camp_wide;
set camp_wide2;
run; *<-saving;

*Grab a Random Sample of 8 subjects;
proc surveyselect
data=c.camp_wide
method=srs
rep=1
sampsize=8
seed=764768
out=camp8;
id _all_;
run;

data camp8_long; *<-------Convert back to long_format;
set camp8;
visitc=0; posfev=posfev_wide0; output;
visitc=2; posfev=posfev_wide2; output;
visitc=4; posfev=posfev_wide4; output;
visitc=12; posfev=posfev_wide12; output;
visitc=16; posfev=posfev_wide16; output;
visitc=24; posfev=posfev_wide24; output;
visitc=28; posfev=posfev_wide28; output;
visitc=36; posfev=posfev_wide36; output;
visitc=40; posfev=posfev_wide40; output;
```

```
visitc=44; posfev=posfev_wide44; output;
visitc=48; posfev=posfev_wide48; output;
visitc=52; posfev=posfev_wide52; output;
visitc=60; posfev=posfev_wide60; output;
visitc=64; posfev=posfev_wide64; output;
visitc=72; posfev=posfev_wide72; output;
visitc=84; posfev=posfev_wide84; output;
visitc=96; posfev=posfev_wide96; output;
visitc=108; posfev=posfev_wide108; output;
visitc=120; posfev=posfev_wide120; output;
drop posfev_wide0 - posfev_wide120;
run;

proc sgpanel data = camp8_long; *<------- Profile plots;
panelby id / columns=4 rows=2;
pbspline y = posfev x = visitc;
run;

proc sgpanel data = camp8_long;
panelby id / columns=4 rows=2;
reg y = posfev x = visitc;
run;

*************************************************************************
                        Scatter and Spaghetti Plots
*************************************************************************;

*Scatter plot;
proc sgplot data=c.camp;
scatter x=visitc_num y=posfev;
reg x=visitc_num y = posfev / nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*PBspline;
proc sgplot data=c.camp;
series x=visitc_num y=posfev / group=id
lineattrs=(color=gray pattern=1
thickness=1);
pbspline x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*linear;
proc sgplot data=c.camp;
```

```
reg x=visitc_num y=posfev / nomarkers group=id
lineattrs=(color=gray pattern=1
thickness=1);
reg x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*Spaghetti plots by covariates;
* Treatment A;
*PBspline;
proc sgplot data=c.camp;
Title "A";
where tg = "A";
series x=visitc_num y=posfev / group=id
lineattrs=(color=gray pattern=1
thickness=1);
pbspline x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*linear;
proc sgplot data=c.camp;
Title "A";
where tg = "A";
reg x=visitc_num y=posfev / nomarkers group=id
lineattrs=(color=gray pattern=1
thickness=1);
reg x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

* Treatment B;

*PBspline;
proc sgplot data=c.camp;
Title "B";
where tg = "B";
series x=visitc_num y=posfev / group=id
lineattrs=(color=gray pattern=1
thickness=1);
pbspline x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
```

```
run;

*linear;
proc sgplot data=c.camp;
Title "B";
where tg = "B";
reg x=visitc_num y=posfev / nomarkers group=id
lineattrs=(color=gray pattern=1
thickness=1);
reg x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

* Treatment C;

*PBspline;
proc sgplot data=c.camp;
Title "C";
where tg = "C";
series x=visitc_num y=posfev / group=id
lineattrs=(color=gray pattern=1
thickness=1);
pbspline x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*linear;
proc sgplot data=c.camp;
Title "C";
where tg = "C";
reg x=visitc_num y=posfev / nomarkers group=id
lineattrs=(color=gray pattern=1
thickness=1);
reg x=visitc_num y=posfev
/ nomarkers lineattrs=(color=red
pattern=1 thickness=3);
run;

*************************************************************************
                          Table 1 and Table 2
*************************************************************************;

*Overall sample;
proc means data=c.camp_teach;
```

```
where visitc = "000";
var age_rz hemog agehome wbc;
run;
proc freq data=c.camp_teach;
where visitc = "000";
tables ethnic
gender tg any_smokes anypet dehumid parent_smokes woodstove;
run;

* Table 1 Strata;
*Treatment A;
proc means data=c.camp_teach;
where visitc = "000" AND tg = "A";
var age_rz hemog agehome wbc;
run;
proc freq data=c.camp_teach;
where visitc = "000" AND tg = "A";
tables ethnic
gender tg any_smokes anypet dehumid parent_smokes woodstove;
run;
*Treatment B;
proc means data=c.camp_teach;
where visitc = "000" AND tg = "B";
var age_rz hemog agehome wbc;
run;
proc freq data=c.camp_teach;
where visitc = "000" AND tg = "B";
tables ethnic
gender tg any_smokes anypet dehumid parent_smokes woodstove;
run;
*Treatment C;
proc means data=c.camp_teach;
where visitc = "000" AND tg = "C";
var age_rz hemog agehome wbc;
run;
proc freq data=c.camp_teach;
where visitc = "000" AND tg = "C";
tables ethnic
gender tg any_smokes anypet dehumid parent_smokes woodstove;
run;

*Table 2;
proc freq data = c.camp_teach;
title "Table 2";
tables visitc;
run;
```

```
*****************************************************************
                        Comparing Models
*****************************************************************;

*****************************************************
                        Comparing Models A B
*****************************************************;
proc mixed data=c.camp method=ml covtest; *<----- Unconditional Means
Model;
title "Model A Unconditional Means Model";
class id;
model posfev =/solution notest;
random intercept/sub=id;
run;
*Time is visitc_num;
proc mixed data=c.camp method=ml; *<----- Unconditional Growth
Model;
title "Model B Unconditional Growth Model with visitc";
class id visitc;
model posfev = visitc_num/solution notest outpm=pred;
random intercept visitc_num/ type=un sub=id;
run;
*************************************************************
WARNING both unconditional growth models were unable to
make Hessian positive definite. Mean estimates cannot be trusted!
Solution: Take a random variance component out of the model and run
again
Since the slopes and variance component for slope have standard errors
of 0
take TIME out of the random statement.
*************************************************************;

*hypothesis testing models A vs B;
data calc;
pvisitc_num = 1- probchi(18976.5,3);
run;
proc print data=calc;
run;
*****************************************************
     Visitc_num has better properties than fdays
     Continue with vitistc_num
*****************************************************;

*****************************************************
```

```
                Comparing Models B C
*****************************************************;
*Model B: Visitc;
proc mixed data=c.camp method=ml covtest;
title "Model B Unconditional Growth Model with visitc_num";
class id;
model posfev = visitc_num/solution notest;
random intercept visitc_num/ type=un sub=id;
run;
*Model C: Visitc + TG;
proc mixed data=c.camp method=ml;
title "Model C visitc_num + TG";
class id tg;
model posfev = visitc_num TG visitc_num*TG /solution notest;
random intercept visitc_num/ type=un sub=id;
run;
data calc;
pvisitc_num = 1- probchi(4430.8 - 4419.7,1);
run;
proc print data=calc;
run;

*****************************************************
                Comparing Models C and D
*****************************************************;
*Model C: Visitc + TG;
proc mixed data=c.camp method=ml;
title "Model C visitc_num + TG";
class id tg;
model posfev = visitc_num TG visitc_num*TG /solution notest;
random intercept visitc_num/ type=un sub=id;
run;
*Model D: Visitc + TG + age_rz;
proc mixed data=c.camp method=ml;
title "Model D visitc_num + TG + age_rz";
class id tg;
model posfev = visitc_num TG age_rz visitc_num*TG visitc_num*age_rz /s
olution notest;
random intercept visitc_num/ type=un sub=id;
run;
data calc;
pvisitc_num = 1- probchi(4419.7 - 4415.2,1);
run;
proc print data=calc;
run;
```

```
*Model C is better. Stick with model C;


*****************************************************
           Comparing Models C and E
*****************************************************;
*Model C: Visitc + TG;
proc mixed data=c.camp method=ml;
title "Model C visitc_num + TG";
class id tg;
model posfev = visitc_num TG visitc_num*TG /solution notest;
random intercept visitc_num/ type=un sub=id;
run;
*Model E: Visitc + TG + age_rz;
proc mixed data=c.camp method=ml;
title "Model D visitc_num + TG + age_rz";
class id tg gender;
model posfev = visitc_num TG
gender visitc_num*TG visitc_num*gender /solution notest;
random intercept visitc_num/ type=un sub=id;
run;
data calc;
pvisitc_num = 1- probchi(4419.7 - 4418.5,1);
run;
proc print data=calc;
run;

*********************************************************************
                Comparing Error covariance Matrixes
*********************************************************************;

*Independence model;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: ind";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=simple sub=id r rcorr;
ods output fitstatistics = fitstat_ind;
run;

*Unstructured model;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: un";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=un sub=id r rcorr;
```

```
ods output fitstatistics = fitstat_un;
run;

*Compound Symmetry;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: cs";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=cs sub=id r rcorr;
ods output fitstatistics = fitstat_cs;
run;

*Hetereo Compound Symmetry;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: csh";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=csh sub=id r rcorr;
ods output fitstatistics = fitstat_csh;
run;

*First order autoregressive structure;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: ar(1)";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=ar(1) sub=id r rcorr;
ods output fitstatistics = fitstat_ar;
run;

*heterogenous autoregressive;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: ar(1)h";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=arh(1) sub=id r rcorr;
ods output fitstatistics = fitstat_arh;
run;

*toeplitz;
proc mixed data=c.camp method=reml covtest;
title "Model C visitc_num + TG; Error Structure: toep";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
repeated waves/ type=toep sub=id r rcorr;
ods output fitstatistics = fitstat_toep;
```

```
run;
*standard multilevel model;
proc mixed data=c.camp;
title "Model C visitc_num + TG; Error Structure: std";
class id tg waves;
model posfev = visitc_num TG visitc_num*TG /solution notest;
random intercept visitc_num/type=un sub=id;
ods output fitstatistics = fitstat_Std;
run;

************************************************
Renaming "value" column of fit statistics table
************************************************;
data one;
set fitstat_ind;
IND = value;
drop value;
run;
data two;
set fitstat_std;
STD = value;
drop value;
run;
data three;
set two;
UN = "No Fit"; *<---------- Model did not converge
using unstructured;
drop STD;
run;
data four;
set fitstat_cs;
CS = value;
drop value;
run;
data five;
set fitstat_csh;
CSH = value;
drop value;
run;
data six;
set fitstat_ar;
AR = value;
drop value;
run;
data seven;
set fitstat_arh;
```

```
ARH = value;
drop value;
run;
data eight;
set fitstat_toep;
TOEP = value;
drop value;
run;
************************************************;


************************************************
                Merging fit statistics
************************************************;
data compare_covar_struc;
merge one two three four five six seven eight;
by Descr;
run;
proc print data=compare_covar_struc;
run;
*****************************************
Heterogenous Autoregressive was the best fit
We need a correlation matrix to provide
evidence of band symmetry
*****************************************;

*********************************************************************

Create a Correlation Matrix of Measurement Occasions Using Wide
Format
*********************************************************************;

data new;
set c.camp_wide;
rename posfev_wide2 = Measurement1;
rename posfev_wide4 = Measurement2;
rename posfev_wide12 = Measurement3;
rename posfev_wide16 = Measurement4;
rename posfev_wide24 = Measurement5;
rename posfev_wide28 = Measurement6;
rename posfev_wide36 = Measurement7;
rename posfev_wide40 = Measurement8;
rename posfev_wide44 = Measurement9;
rename posfev_wide48 = Measurement10;
rename posfev_wide52 = Measurement11;
rename posfev_wide56 = Measurement12;
```

```
rename posfev_wide60 = Measurement13;
rename posfev_wide64 = Measurement14;
rename posfev_wide72 = Measurement15;
rename posfev_wide84 = Measurement16;
rename posfev_wide96 = Measurement17;
rename posfev_wide108 = Measurement18;
rename posfev_wide120 = Measurement19;
run;
proc corr data=new;
var Measurement1
Measurement2
Measurement3
Measurement4
Measurement5
Measurement6
Measurement7
Measurement8
Measurement9
Measurement10
Measurement11
Measurement12
Measurement13
Measurement14
Measurement15
Measurement16
Measurement17
Measurement18
Measurement19 ;
run; *<--- There is evidence of band symmetry.


*************************************************************************
                        Running the Final Model
*************************************************************************;

proc mixed data=c.camp method=ml covtest;
title "Model C visitc_num + TG";
class id tg;
model posfev = visitc_num TG visitc_num*TG /solution notest;
random intercept visitc_num/ type=arh(1) sub=id;
run;

*************************************************************************
           Create the Model Plot with Annotations
*************************************************************************;
```

```
proc import datafile="/home/u49993673/CAMP/annocamp.csv"
dbms=csv
out=c.annocamp
replace; *<--- Import annotation dataset;
getnames=yes;
run;
data camp;
set c.camp;
time = visitc_num / 12 ;
time_cat = time;
run;
proc mixed data=camp method=ml covtest;
title "heterogenous autoregressive Error
Covariance Matrix";
class id TG time_cat;
model posfev = time TG time*TG/solution notest;
random intercept time/type=arh(1) sub=id;
estimate "posfev at follow up year 0 in
A" intercept 1 TG 1 0 0 time 0 TG*time 0 0 0 /cl;
estimate "posfev at follow up year 0 in
B" intercept 1 TG 0 1 0 time 0 TG*time 0 0 0 /cl;
estimate "posfev at follow up year 0 in
C" intercept 1 TG 0 0 1 time 0 TG*time 0 0 0 /cl;
estimate "posfev at follow up year 5 in
A" intercept 1 TG 1 0 0 time 5 TG*time 5 0 0 /cl;
estimate "posfev at follow up year 5 in
B" intercept 1 TG 0 1 0 time 5 TG*time 0 5 0 /cl;
estimate "posfev at follow up year 5 in
C" intercept 1 TG 0 0 1 time 5 TG*time 0 0 5 /cl;
estimate "posfev at follow up year 10 in
A" intercept 1 TG 1 0 0 time 10 TG*time 10 0 0 /cl;
estimate "posfev at follow up year 10 in
B" intercept 1 TG 0 1 0 time 10 TG*time 0 10 0 /cl;
estimate "posfev at follow up year 10 in
C" intercept 1 TG 0 0 1 time 10 TG*time 0 0 10 /cl;
ods output estimates= est;
run;
data camp_est;
set est;
if _n_ < 7 then do;
TG = substr(label, 31, 1);
TIME = substr(label,26, 1)* 1.0;
end;
else do;
TG = substr(label, 32, 1);
TIME = substr(label,26, 2) * 1.0;
```

```
end;
keep label estimate StdErr tg time upper lower;
run;
PROC FORMAT;
VALUE $Treatment "A"="Budesonide" "B"="Nedocromil" "C"="Albuterol
(Placebo)";
RUN;

*Run SGpLot with annotation;
proc sgplot data=camp_est nowall sganno=c.annocamp;
format tg $treatment.;
title "Fev1 Rate of Growth Over 10 Years";
styleattrs datacontrastcolors=(purple green orange)
datalinepatterns=(solid)
backcolor=whitesmoke
;
reg y=estimate x=time / cli cliattrs=(CLILINEATTRS=(pattern=2 thicknes
s=1)) lineattrs=(pattern=1
thickness=0.01)
nomarkers group=TG;
scatter y=estimate x=time/ group=TG yerrorlower=lower yerrorupper=uppe
r
markerattrs=(symbol=Circlefilled size=5);
yaxis min=0 max=4;
xaxis display=(nolabel noline noticks) valueattrs=(color=black) values
= (0 to 10 by 1);
yaxis display=(nolabel noline noticks) valueattrs=(color=black);
yaxis label="FEV1 After Treatment (liters per
sec)" labelattrs=(weight=bold) valueattrs=(color=black weight=bold)
values=(1.5, 2, 2.5, 3, 3.5,4, 4.5);
xaxis label="Years Since Randomization" labelattrs=(weight=bold)
values =(0,1,2,3,4,5,6,7,8,9,10);
run;

*************************************************************
          Supplemental Graph with Categorical Time
*************************************************************;
data camp;
set c.camp;
time = visitc_num / 12 ;
time_cat = time;
run;
proc means data=camp mean stderr;
where time in (0, 5, 10);
var posfev ;
class tg time;
```

```
ods output summary=mean_est;
run;
data mean_est2;
set mean_est;
left= posfev_mean-posfev_stdErr;
right= posfev_mean+posfev_stdErr;
run;
*sganno=annotest7;
proc sgplot data=mean_est2 nowall;
styleattrs datacontrastcolors=(purple green orange)
datalinepatterns=(solid)
backcolor=whitesmoke
;
xaxis label="Years Since Randomization" values= (0 to 10 by 1);
yaxis label="FEV1 After Treatment (liters per sec)" min=0 max=4;
scatter y=posfev_mean x=time/ group=TG yerrorlower=left yerrorupper=ri
ght
markerattrs=(symbol=CircleFilled);
series x=time y=posfev_mean /
group=TG
lineattrs=(pattern=2);
run;
```