Longitudinal Effects of Asthma Treatments on Pulmonary Function in Children: A Fixed Model Analysis of the CAMP Study

BS857, Spring 2025

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Introduction

Asthma is one of the most common chronic conditions among children worldwide, and effective long-term management remains a public health priority. The Childhood Asthma Management Program (CAMP) was a randomized controlled trial investigating the effects of daily inhaled treatments—budesonide (A), nedocromil (B), and placebo (C)—on pulmonary function in children aged 5 to 12 with mild-to-moderate asthma ("The Childhood Asthma", 1999). The dataset includes repeated measures of post-bronchodilator FEV1 (POSFEV) across multiple clinic visits, along with demographic and environmental covariates.

In this project, we use linear mixed-effects models to evaluate whether treatment type influences FEV1 over time. FEV1 is a measure of air volume a person exhales from lungs within 1 second after maximal inhalation and indicates pulmonary function (David, 2024). Time was modeled using *visitc*, a categorical variable representing scheduled follow-up visits. This analysis involved selecting meaningful baseline covariates, exploring interaction effects, checking variable distributions, and identifying the best-fitting covariance structure. Our goal was to build a streamlined, clinically relevant model that captures both individual variation and treatment effects over time. Additionally, we aim to test if either of the daily inhaled treatments had a greater mean increase of post-bronchodilator FEV1 in study participants than the placebo.

Methods

We began by conducting literature review to determine study goals and evaluate clinical relevance of given variables in the dataset. We finalized our project goals of building a model to test if the treatments have a greater mean increase in post-bronchodilator FEV1 compared to the placebo, which is similar to the goal of the original CAMP study ("The Childhood Asthma", 1999). Therefore, we wanted to build a model with post-bronchodilator FEV1 as the outcome variable and treatment group as the main predictor. In determining covariates, we decided to

adjust for baseline covariates as the original CAMP study also did, which includes variables age, gender, and ethnic group ("The Childhood Asthma", 1999). There were other variables available in our dataset that could be related to asthma and thus post-bronchodilator FEV1, as pets, smoking from parents or others, use of dehumidifier, and use of woodstove. From literature review, we found that environmental factors can affect asthma so we considered the aforementioned variables as potential covariates ("National Asthma Education", 2007). We also considered the variable representing hemoglobin levels as a potential covariate after finding a study that found a significant association between anemia (low hemoglobin levels) and asthma in children (Ramakrishnan & Borade, 2010).

Following literature review, we conducted exploratory data analysis on our dataset. First, we found in our research that lethal hemoglobin levels are below 5 g/dl and found that two subjects had hemoglobin levels below 2 g/dl ("Nursing Critical Care", 2020). Since these measurements clinically do not make sense, we removed the two subjects from all future analyses. Characteristics at randomization were reviewed to assess imbalances(Appendix, Table 1). Selected characteristics appeared balanced across treatment groups except for sex where group A was 41% female, group B was 33% female, and group C was 47% female. The density and Q-Q plot for POSFEV reveal a right-skewed distribution(Appendix, Figures 1,2). As such, we can use PROC MIXED which handles mixed effects with general linear models. The distribution for hemoglobin initially raised concerns for bimodality, however the Q-Q plot was normal(Appendix, Figures 3,4). POSFEV was noticeably correlated with visit (0.68) and mildly correlated with hemoglobin (0.19), indicating change over time (Appendix, Figure 5). Similarly, box plots of POSFEV across treatment groups at randomization, 56 months, and 120 months show an increasing trend in POSFEV over time with similar medians in each group for each snapshot (Appendix, Figure 6). Spaghetti plots also support similar increasing trends over time between groups with no knots (Appendix, Figure 7).

We evaluated potential covariates for inclusion in the mixed-effects model using the *PROC MIXED* procedure in SAS. Covariates were selected based on baseline availability, clinical relevance supported by prior asthma literature, and statistical contribution to model performance. Pearson correlation matrices were used to assess multicollinearity, and variables with high

correlation ($\rho > 0.8$) were not included together to avoid redundancy. Variables that consistently lacked statistical significance ($p > 0.1$) or did not improve model fit as assessed by AIC and BIC were excluded.

Once covariates were finalized, an appropriate variance covariance structure was identified by comparing maximized REML log likelihoods between models using unstructured, heterogeneous compound symmetry, compound symmetry, heterogeneous autoregressive, and 1st order autoregressive covariance structures. Nested models were compared via a likelihood ratio test while non-nested models were compared via AIC/BIC.

Correlation between repeated visits for patients was accounted for through a *repeated* statement. Another method of accounting for correlation of visits between subjects was through the incorporation of random effects, and models were compared using BIC. Initially, missing observations were excluded and the model was run with the complete cases (CC). To utilize our full set of observations, multiple imputation (MI) was performed to produce 10 complete datasets, and estimates were combined using the *PROC MIANALYZE* procedure. Type 3 tests were combined from MI using *MACRO COMBCHI* created by Paul Allison (2004). Estimates from the MI were compared with estimates from the complete case (CC) analysis to determine robustness of results.

Results

After testing multiple combinations and evaluating model fit, the following variables were retained for adjustment in the initial model:
Baseline Hemoglobin was retained due to strong and consistent statistical significance ($p < 0.0001$). Age at baseline (*AGE_RZ*), gender (*GENDER*), and ethnicity (*ETHNIC*) were included to adjust for demographic differences based on prior studies, though none were individually significant. Highly correlated environmental exposures (*parent_smokes and any_smokes*, $\rho = 0.96$) were evaluated, and parent_smokes was initially retained as a more direct measure of chronic exposure. However, it was excluded from the final model due to lack of significance ($p =$

0.123). Other environmental factors like *agehome*, *dehumid*, *woodstove*, *anypet*, and *wbc* were excluded for same reason.
This final covariate structure was used in subsequent models analyzing treatment effects.

Comparison of maximized REML log-likelihoods between nested covariance structures showed that the heterogeneous compound symmetry (HCS) model fit better than the compound symmetry model (LR Chi Square = 2428.7 on 19DF, $p < .0001$) and that the heterogeneous first-order autoregressive (HAR(1)) structure fit better than the first-order autoregressive structure (LR Chi Square = 2013.2 on 19 DF, $p < .0001$). Comparison of REML-estimated AIC between the HCS model (AIC = 5600.4) and the HAR(1) models (AIC = 92.8) showed that the HAR(1) covariance structure fit the data best.

Reevaluating covariates after the covariance structure was fit, the variables that best explain our data in a fixed effects model were the main effects of treatment, visit, age, and gender, and the effect modifications of treatment by visit and gender (BIC = 220.6).

In the mixed effect model with the fixed effects specified above and a random intercept with structure HAR(1) as discovered prior, we found the mixed effects model fit the data worse than the fixed effects model (BIC of mixed effects = 8128.4, BIC of fixed effects = 220.6). Additionally, we attempted to run a mixed effect model keeping the same fixed effects, but with a random intercept and random slope for visit. The model failed to converge, indicating some counts of visit were not large enough to estimate a slope. This was confirmed through the distribution of follow-up visits - visits at month 44 (n = 10), month 64 (n = 19), and month 120 (n = 73) had low counts of patients who followed-up at that visit (Appendix, Figure 8). Therefore, it is not appropriate to move forward with a mixed effects model. Our analysis and conclusion will focus on the fixed effects model.

When examining missing data patterns, we found three sets of observations in the data that have the same pattern of missingness. 9782 observations (98.65%) have a complete set of information. 97 observations (0.98%) are missing information on hemoglobin. 37 observations (0.37%) are missing information on POSFEV. Since the distributions of missing data patterns differ between

groups in terms of visit, we should move forward with the assumption that missingness is not completely at random and perform multiple imputation (Appendix, Table 2). The proportion of missing in our data is 0.003. If we run imputation ten times, we can recover approximately 99.97% of our data.

From the combination of MI results, we found neither treatment significantly improved POSFEV for study participants compared to the placebo when adjusting for multiple testing ($\beta_A = 1.25$, 95% CI: 0.02, 2.49, $p = 0.05$; $\beta_B = 0.11$, 95% CI: -1.30, 1.53, $p = 0.86$). Additionally, female gender significantly decreased POSFEV compared to male gender ($\beta_{Female} = -0.14$, 95% CI: -0.23, -0.04). Also, each unit increase of hemoglobin increases POSFEV by about 0.17 units (95% CI: 0.08, 0.26) and this finding is statistically significant ($T = 4.54$, $p = 0.005$). Each unit increase in age significantly increased post_FEV1 by about 0.02 ($p = 0.01$). Lastly, we find that the treatment effect changes over time ($F = 6.29$, $df = 9$, $p = < 0.00001$). Results in the MI are less significant than discovered in CC (Appendix, Table 2).

Conclusions and Discussion

With the adjustment of baseline covariates, there is no significant evidence that budesonide or nedocromil improved post-bronchodilator FEV1 for children with asthma in this study compared to the placebo. The effect of treatments appear to differ over time and with gender and hemoglobin status. Hemoglobin was significantly associated with better POSFEV values, while female participants exhibited slightly lower lung function compared to males.

We were limited in our model effects selections due to low counts within visits, which prevented stable estimation of random slopes for time. As a result, the final model focused on fixed effects. Future work could explore more flexible longitudinal models to better capture individual variation across longer follow-up periods.

References

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Appendix

Table 1. Characteristics by Treatment Group at Randomization

	A (N=205)	B (N=207)	C (N=272)	Overall (N=684)
Age in years at Randomization				
Mean (SD)	8.50 (2.14)	8.30 (2.15)	8.32 (2.17)	8.37 (2.16)
Median [Min, Max]	8.00 [5.00, 13.0]	8.00 [5.00, 13.0]	8.00 [5.00, 13.0]	8.00 [5.00, 13.0]
Sex				
Female	83 (40.5%)	68 (32.9%)	128 (47.1%)	279 (40.8%)
Male	122 (59.5%)	139 (67.1%)	144 (52.9%)	405 (59.2%)
Race/Ethnicity				
White	138 (67.3%)	142 (68.6%)	193 (71.0%)	473 (69.2%)
Black	27 (13.2%)	25 (12.1%)	33 (12.1%)	85 (12.4%)
Hispanic	19 (9.3%)	23 (11.1%)	25 (9.2%)	67 (9.8%)
Other	21 (10.2%)	17 (8.2%)	21 (7.7%)	59 (8.6%)
Hemoglobin (g/dl)				
Mean (SD)	13.2 (0.960)	13.2 (0.995)	13.1 (0.948)	13.2 (0.965)
Median [Min, Max]	13.1 [10.6, 16.7]	13.1 [10.8, 15.6]	13.2 [10.5, 15.8]	13.2 [10.5, 16.7]

Figure 1. POSFEV Density Plot

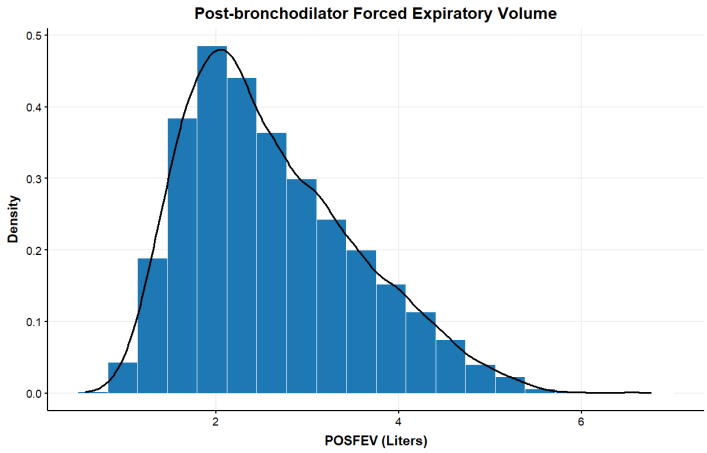

Figure 2. POSFEV Q-Q Plot

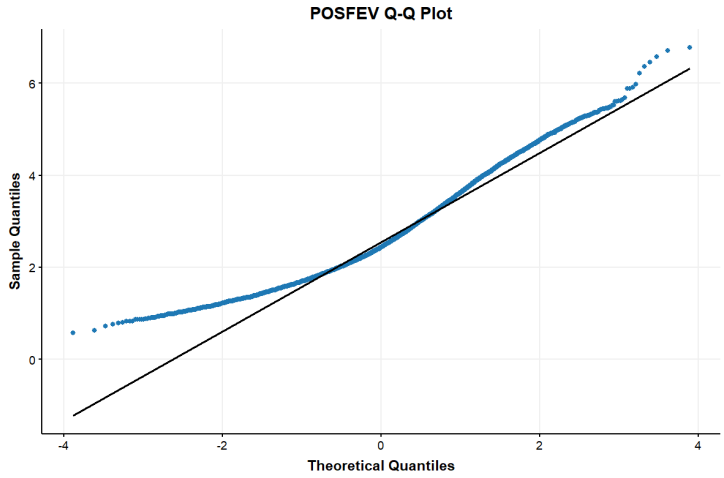

Figure 3. Distribution of Follow-Up Visits (in months)

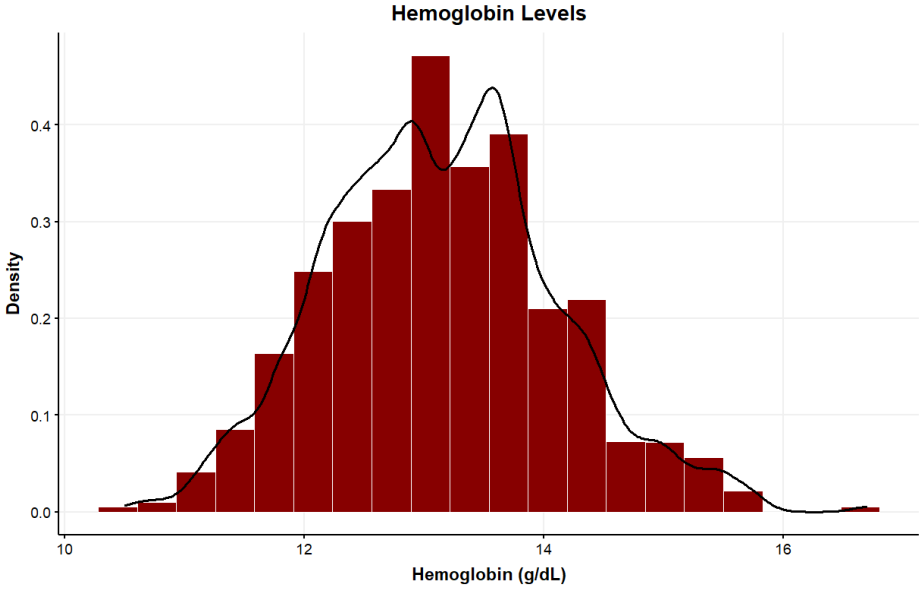

Figure 4. Distribution of Follow-Up Visits (in months)

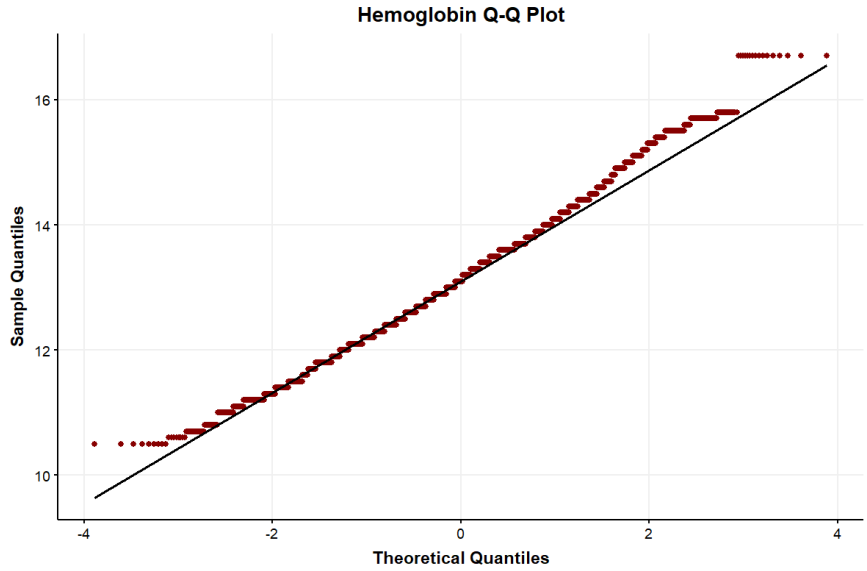

Figure 5. Distribution of Follow-Up Visits (in months)

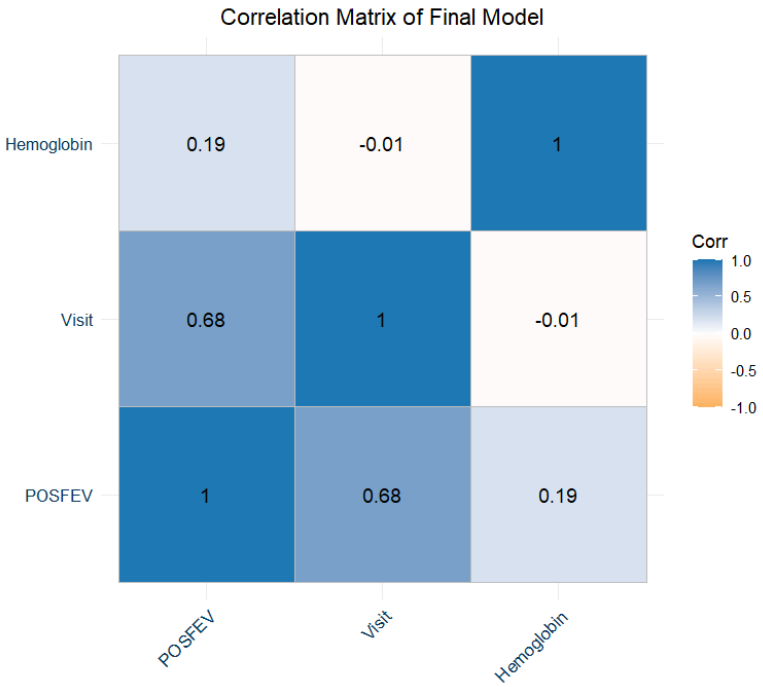

Figure 6. Distribution of Follow-Up Visits (in months)

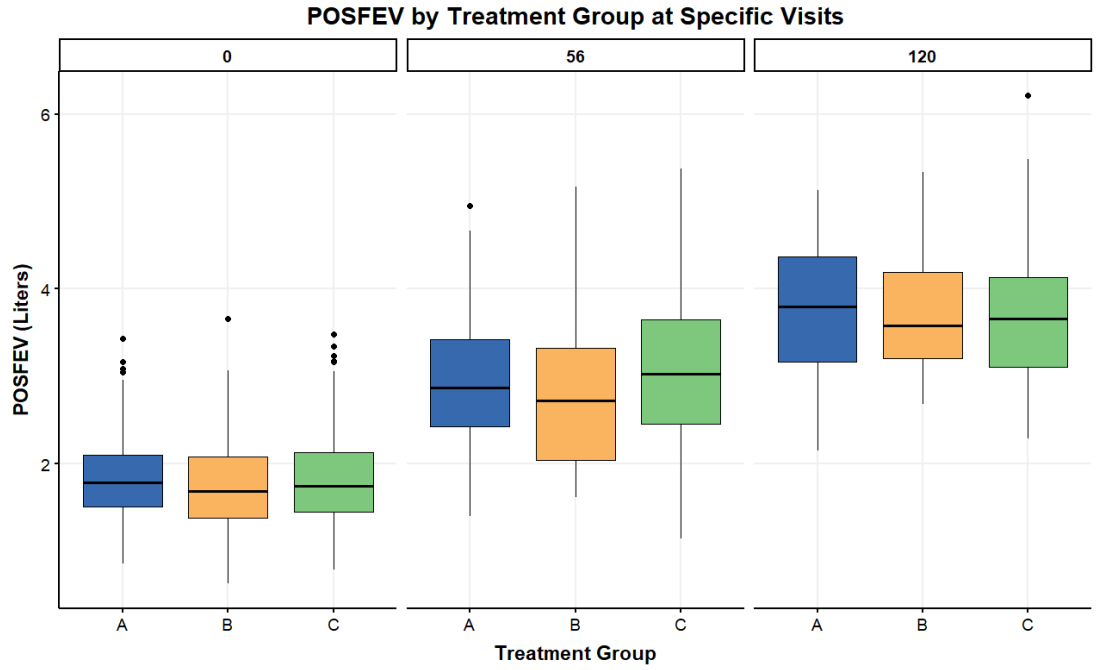

Figure 7. Distribution of Follow-Up Visits (in months)

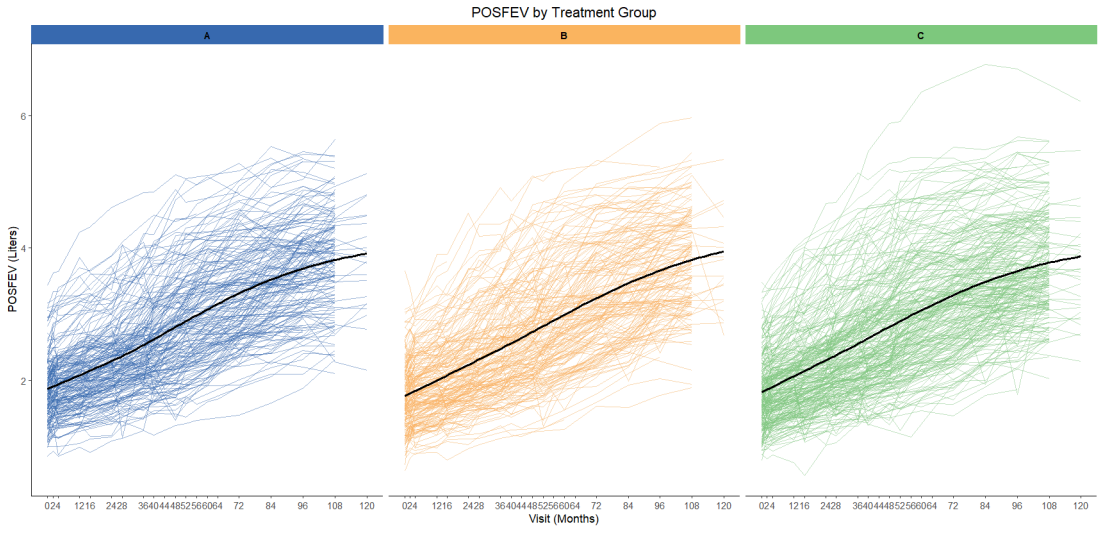

Figure 8. Distribution of Follow-Up Visits (in months)

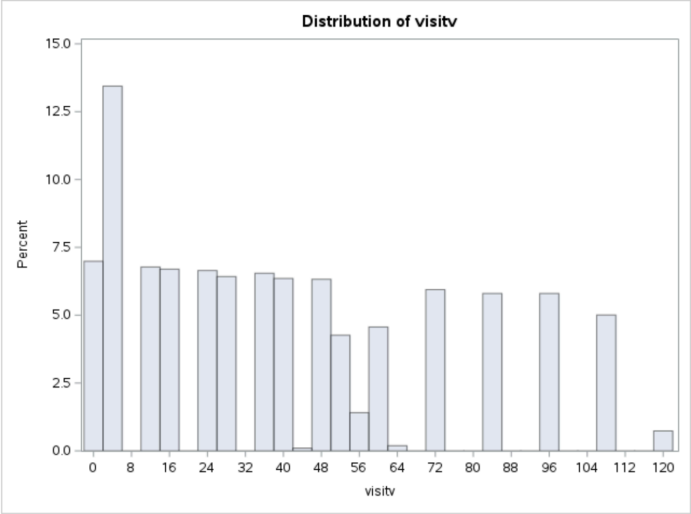

Table 2: Missing data pattern

Group	POSFEV	TG	Age	Gender	Ethnicity	Hemo	Visit	Freq (%)
1	X	X	X	X	X	X	X	9782 (98.65)
2	X	X	X	X	X	.	X	97 (0.98)
3	.	X	X	X	X	X	X	37 (0.37)

Table 3. Comparing Estimates from Multiple Imputation (MI) to Complete Case (CC) Analysis

	MI Estimate	MI T-Stat (p)	CC Estimate	CC T-Stat (p)
Intercept	0.52 (-1.73, 0.70)	-1.04 (0.34)	-1.33 (-1.96, -0.71)	-4.17 (<0.0001)
TG				
A	1.25 (0.02, 2.49)	2.30 (0.05)	1.45 (0.50, 2.39)	3.00 (0.003)
B	0.11 (-1.30, 1.53)	0.18 (0.86)	-0.14 (1.06, 0.78)	-0.30 (0.77)
Gender, Female	-0.14 (-0.23, -0.04)	-3.01 (0.006)	-0.15 (-0.24, -0.06)	-3.30 (0.001)
Hemoglobin	0.17 (0.08, 0.26)	4.54 (0.005)	0.23 (0.19, 0.28)	9.81 (< 0.0001)
Age	0.02 (0.005, 0.03)	2.78 (0.0099)	0.02 (0.007, 0.03)	2.97 (0.0031)
Visit Omitted Due to Length of Levels				