Stats 210C Final Project

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June 13, 2025

Contents

1 Abstract

Serum beta-carotene was measured monthly in 46 adults randomized to placebo, 15, 30, 45, or 60 mg/day beta-carotene for 6 months and followed for 6 months post treatment. Supplementation raised the 6-month average concentration by about 965 $\mu g/mL$ versus the placebo (95% CI 638, 1,291; P = 7.9×10^{-5}); the rise varied by dose (P = 0.040) and was steeper in men than women ($\chi^2 = 23.9$; P = 0.032) but was not modified by age, BMI or cholesterol (all P $\geq$ 0.52). After treatment stopped, levels fell by 105 $\mu g/mL$ a month (95% CI −417, -206) with no dose-specific difference in return to baseline rate after supplementation (P $\geq$ 0.09). Predictions showed continued dosing for three additional months would maintain a dose dependent separation across groups. Small sample size, intermittent missing visits and unmeasured dietary intake limit generalizability, but the data provides strong evidence that beta-carotene supplementation elevates serum levels in a dose-dependent manner but rates once on and off treatment stabilize.

2 Introduction

The scientific motivation for this analysis centers on understanding the pharmacokinetic properties of beta-carotene supplementation before advancing to large-scale clinical trials. Pharmacokinetics refers to how the body processes a drug over time. More specifically, how different doses affect blood concentrations, the time course of drug accumulation, potential interactions with other blood components, and the rate of clearance once treatment stops.

Beta-carotene has generated interest as a potential cancer prevention agent, making it crucial to characterize its behavior in human subjects. The study employed a randomized, double-blind design with 46 volunteers receiving one of five beta-carotene doses (0, 15, 30, 45, or 60 mg/day) over a carefully structured timeline. The dosing protocol included a 4-month placebo run-in period (months 0-3), followed by 6 months of active treatment (months 4-9), and then 6 months of post-treatment observation (months 10-15).

The primary research question focused on determining how different beta-carotene dose levels influence serum beta-carotene concentrations over time. Additionally, investigators were interested in whether beta-carotene supplementation affects vitamin E levels, given that both compounds are lipid-soluble and might compete for similar absorption or transport mechanisms in the body.

The goal of the analysis is to characterize how beta-carotene supplementation and its dose, alter serum beta-carotene profiles over time, and explores whether these dynamics depend on patient characteristics. More specifically, we use the study data to address the following scientific questions:

- Time Averaged Change: Is supplementation associated with a higher time-averaged serum beta-carotene level, and does this effect depend on dose?
- Longitudinal trajectory: How does supplementation influence the month-by-month pattern of serum beta-carotene, and is any temporal effect dose-dependent?
- Return to Baseline: If supplementation elevates beta-carotene, do different doses lead to differential rates of decline back to baseline once treatment stops?
- Effect Modification: Do age, gender, BMI or baseline cholesterol modify the longitudinal effect of supplementation on serum beta-carotene?
- Continued Dosage Predictions: For two example participants at each dose level, what beta-carotene concentrations would be expected had treatment continued for an additional three months?

These questions frame the rest of the report. The next section details the data sources and statistical methods chosen to align with each objective. Later sections present results and their implications for beta-carotene pharmacology.

3 Methods

3.1 Source of the Data

The data originates from a Phase II clinical trial designed to investigate the pharmacokinetics of beta-carotene supplementation. The study employed a randomized, double-blind, placebo-controlled design with 46 volunteers who were randomly assigned to one of five treatment groups (0, 15, 30, 45, or 60 mg/day beta-carotene).

The study used random assignment of participants to dose groups, though the specific recruitment methods and eligibility criteria for the 46 volunteers are not detailed in the provided information. The trial followed a structured longitudinal design with up to 16 scheduled visits per participant over 15 months, creating a repeated measures dataset.

Available Variables:

- id: Patient identifier for tracking individual subjects across visits
- month: Study timepoint (0-15), corresponding to the three-phase design (placebo months 0-3, treatment months 4-9, post-treatment months 10-15)
- bcarot: Serum beta-carotene concentration ($\mu g/mL$) - primary outcome variable
- vite: Serum vitamin E concentration ($\mu g/mL$) - secondary outcome of interest (Will not be included in our models)
- dose: Beta-carotene supplementation dose (0, 15, 30, 45, or 60 mg/day)
- age: Subject age at randomization (years) - potential covariate
- male: Binary indicator for male sex - potential covariate
- bmi: Body mass index (kg/m^2) - potential covariate given lipid-soluble nature of compounds
- chol: Baseline serum cholesterol (mg/dL) - potential covariate relevant to lipid metabolism

3.1.1 Missing data and data integrity

Of the expected $46 \times 16 = 736$ observations, 59 measurements (8%) are missing altogether with 6 more beta-carotene measurements missing within the data, largely because several participants missed one or two follow-up visits. Missingness is scattered across months and doses with no obvious pattern. One coding anomaly was detected being participant 26 being labeled as receiving 30 mg/day when every other month indicates placebo. This value was changed to 0 mg/day before analysis. No other incorrect values (e.g., negative concentrations) were found. Because the amount of missing outcome data is modest and appears unrelated to observed covariates or treatment, analyses use all available observations under a missing-at-random assumption.

3.1.2 Potential confounding and precision variables

Randomization balances measured and unmeasured factors on average, but because dose groups are small, with a sample size around 9, residual imbalance is possible. The following baseline characteristics are therefore treated as potential confounders or precision variables in subsequent models. Age and BMI both may influence lipid-soluble vitamin kinetics. The individuals sex, male or female, may cause differences in fat distribution that could modify absorption. Cholesterol could effect circulating lipoprotein concentration that may affect beta-carotene transport. Unmeasured lifestyle factors (dietary carotenoid intake, smoking

status, alcohol use) are acknowledged as possible unmeasured confoundersn and their absence in the dataset may lead to more cautious interpretation of causal contrasts.

In summary, the dataset offers a large, longitudinal view of serum beta-carotene and vitamin E over three distinct exposure phases, with minimal missingness and clear documentation of key covariates needed to adjust for residual confounding.

3.2 Statistical Methods

All work was carried out in R 4.3.2 via an R-Markdown pipeline to guarantee full reproducibility. Data cleaning and reshaping relied on dplyr and tidyr. Graphics were created with ggplot2 and presentation tables were formatted with kableExtra.. Time-averaged pre-/post differences were tested with base-R Welch two-sample t-tests (t.test) and one-way ANOVA (aov). Longitudinal effects were modelled with lme4 using random intercepts and random slopes. Fixed-effect estimates, Wald confidence intervals and P-values were extracted with broom.mixed. Dose or covariate specific effects were evaluated by likelihood-ratio tests of nested lmer fits (anova(m0, m1)). Non-linear time patterns were accommodated with natural cubic splines from the base-R splines package (ns, interior knots at months 3, 4 and 9).

3.2.1 Question 1: Time-Averaged Change

The goal is to test whether supplementation increases the time-averaged serum beta-carotene during treatment, and whether that increase depends on dose. Increase implies a pre-versus-post comparison so the calculation is post treatment mean minus baseline mean. An individual-level outcome was computed for each participant where I represents each individual. Averaging over several visits reduces variance and gives us a more accurate measurement of each subject's typical beta-carotene level during the relevant period.

$$\Delta_i = (\frac{1}{6}\sum_{m=4}^{9} \beta\text{carot}_{im}) - (\frac{1}{4}\sum_{m=0}^{3} \beta\text{carot}_{im})$$

This difference compares the mean of the six on-treatment measurements (months 4–9) with the mean of the four pre-treatment measurements (months 0–3), directly capturing the increase in time-average. The two tests performed are the two sample t test and one way anova of the post treatment rise. The t test tests the placebo (0 mg) versus any active dose (>= 15 mg) to test if there are clear differences in the effectiveness of the treatment. The one way ANOVA tests dose–response among active doses (15, 30, 45, 60 mg) to see if there are significant changes between doses.

3.2.2 Question 2: Longitudinal Trajectory (LMM)

The goal is to assess how serum beta-carotene changes over time during supplementation, and whether the effect is dose-dependent. Because each participant has repeated measurements, a linear mixed-effects model (LMM) is used to account for within-subject correlation and individual variability. The LMM includes both fixed effects (for time, treatment or dose, and their interaction) and random effects (for subject-specific intercepts and slopes). LMMs are chosen over repeated measures ANOVA or GEE because they flexibly handle missing data and allow for individual-specific trends. P-values and 95% confidence intervals are used to assess statistical significance. Model diagnostics (residuals, Q-Q plots) are used to check assumptions.

For treatment (placebo vs. any dose):

$$Y_{ij} = \beta_0 + \beta_1\text{month}_{ij} + \beta_2\text{treatment}_i + \beta_3(\text{month}_{ij} \times \text{treatment}_i) + b_{0i} + b_{1i}\text{month}_{ij} + \epsilon_{ij}$$

For dose (continuous):

$$Y_{ij} = \beta_0 + \beta_1\text{month}_{ij} + \beta_2\text{dose}_i + \beta_3(\text{month}_{ij} \times \text{dose}_i) + b_{0i} + b_{1i}\text{month}_{ij} + \epsilon_{ij}$$

- Y_{ij} is the serum beta-carotene for individual i at month j (This is the same for all future models)
- β_0 is the overall intercept (This is the same for all future models)
- β_1 is the effect of time (month) and estimates the average monthly change in beta-carotene for the reference group.
- β_2 is the effect of treatment or dose and estimates the difference in beta-carotene between groups at baseline.
- β_3 is the interaction between time and treatment/dose and tests whether the rate of change over time differs by group.
- b_{0i} and b_{1i} are random intercept and slope for individual i Random effects allow each participant to have their own baseline and trajectory. (This is the same for all future models)
- $\epsilon_{ij} \sim \mathrm{N}(0, \sigma^2)$ is the residual error (This is the same for all future models)

3.2.3 Question 3: Return to Baseline (Quadratic Mixed Model)

The goal is to determine whether the rate at which beta-carotene returns to baseline after stopping supplementation differs by dose. The analysis focuses on the post-treatment period (months 10–15) for participants who received any dose. A quadratic mixed-effects model is used to capture potential non-linear (curved) return patterns, with random intercepts and slopes for each subject. If dose * time interactions are not significant, all doses return at similar rates. A quadratic model is used to allow for non-linear washout. Random effects account for individual baseline differences. P-values and confidence intervals are reported. Model diagnostics confirm appropriateness.

$$\begin{aligned} Y_{ij} = \beta_0 + \beta_1(\mathrm{month}_{ij} - 10) + \beta_2(\mathrm{month}_{ij} - 10)^2 + \beta_3\,\mathrm{dose}_i \\ + \beta_4\,\mathrm{dose}_i(\mathrm{month}_{ij} - 10) + \beta_5\,\mathrm{dose}_i(\mathrm{month}_{ij} - 10)^2 + b_{0i} + b_{1i}\mathrm{month}_{ij} + \epsilon_{ij}. \end{aligned}$$

- $(\mathrm{month}_{ij} - 10)$ is time since stopping supplementation (centered at month 10)
- β_1 is the linear effect of time since stopping and describes the average rate of decline after stopping.
- β_2 is the quadratic (curvature) effect and captures acceleration or deceleration in the return to baseline.
- β_3 is the effect of dose and tests whether higher doses start at higher post-treatment levels.
- β_4 is the dose and time interaction: difference in linear decline rate per 15-mg increment. A non-zero value means doses return to baseline at different speeds.
- β_5 is the dose x $time^2$ interaction: difference in curvature of the decline per 15-mg increment.

3.2.4 Question 4: Effect Modification (Spline Mixed Model)

The goal is to test whether the effect of supplementation on beta-carotene differs by baseline covariates (age, gender, BMI, cholesterol). A spline mixed-effects model is used to flexibly model non-linear time trends and to include covariate groupings as fixed effects. Natural splines allow the time effect to change smoothly at specified knots. Splines are used to avoid imposing a linear or quadratic time trend. Random intercepts account for repeated measures. P-values and CIs are reported and model diagnostics confirm fit. A significant covariate effect suggests the response differs by that characteristic.

$$
\begin{aligned}
Y_{ij} \;&= \beta_0 + \sum_{k=1}^{K} (\beta_{1k} + \beta_{2k} T_i + \beta_{3k} C_i + \beta_{4k} T_i C_i) S_k(\text{month}_{ij}) \\
&+ \; (\beta_5 + \beta_6 T_i + \beta_7 C_i + \beta_8 T_i C_i) P_{ij} \\
&+ \; (\beta_9 + \beta_{10} T_i + \beta_{11} C_i + \beta_{12} T_i C_i) P_{ij}^2 \\
&+ \; b_{0i} + \sum_{k=1}^{K} b_{ik}\, S_k(\text{month}_{ij}) + \epsilon_{ij},
\end{aligned}
$$

- $T_i \in \{0, 1\}$: treatment indicator (1 = supplemented, 0 = control)
- C_i: effect-modifier of interest (e.g., *Male* vs *Female*)
- $S_k(\cdot)$: $K = 4$ natural-cubic spline bases with interior knots at months 3, 4, 9
- $P_{ij} = (\text{month}_{ij} - 9)$ and P_{ij}^2: linear & quadratic post treatment terms

Spline segment (months 0 − 9) β_{1k}: Baseline (placebo + ref covariate) non-linear trend, β_{2k}: Extra departure of **treated** group at knot k, β_{3k}: Baseline difference for covariate subgroup C, β_{4k}: *Effect modification*: treatment × C at knot k

Post Treatment Linear β_5: Average post-cessation slope in controls, β_6: Slope change induced by treatment, β_7: Covariate-specific change in slope, β_8 | Treatment × C interaction on slope

Post Treatment curvature $\beta_9, \beta_{10}, \beta_{11}, \beta_{12}$: Same four-way structure for the quadratic (curvature) component

3.2.5 Question 5: Continued Dosage Predictions

The goal is to predict what would happen to serum beta-carotene if supplementation continued for three more months. Using the fitted dose model from Question 2, we generate predictions for two randomly selected participants at each dose, extrapolating their values for months 10–12. Predictions are made using the `predict()` function in R, with new data for future months and the same model structure. The model is the same as in Question 2, but applied to new (future) months. Predicted values represent expected serum beta-carotene if treatment continued. These predictions illustrate the model's utility for clinical planning. Predictions are based on the best-fitting model for the treatment period. Confidence intervals can be generated if needed. This approach is standard for prediction scenarios.

4 Results

4.1 Features of the Data

Table 1 shows that the five randomized groups were well balanced at baseline: sample sizes ranged from 8 to 10, the mean age clustered around 56 years old, BMI around 25–26 kg per height in meter squared and the proportion of males was roughly 50% in every dosage group. The mean and variance of baseline serum beta-carotene was low across doses at about 233–279 micro grams per ml, showing successful randomization. This included all individuals despite some having missing values at certain weeks and a subject at Dose 0 having a seemingly incorrectly inputted dosage of 30 instead of 0. Figure 1A displays all 46 individual trajectories from month 0 to 15. However, it did remove the individuals with missing values. We can see more clearly from Figure 1B, the means, that all curves sit near baseline until treatment starts at month 4. From there we can see they separate drastically as placebo lines remain flat versus where higher-dose lines climb steeply during months 4-9 and then decline once supplementation stops (months 10-15). By month

15 they all almost returned to baseline but still remained higher than the placebo group despite being off the doses for months. This visual pattern suggests that supplementation elevates beta-carotene and that the rise depends on dose.

Table 1: Baseline characteristics by randomized dose

	level	0	15	30	45	60	p	test
n		9	10	9	8	10		
age (mean (SD))		56.11 (4.04)	56.30 (4.64)	57.44 (4.25)	55.88 (3.14)	56.50 (5.21)	0.953	
bmi (mean (SD))		26.18 (3.59)	25.69 (3.58)	25.83 (2.66)	25.35 (3.32)	24.94 (2.43)	0.931	
chol (mean (SD))		216.00 (27.17)	223.00 (29.72)	214.44 (35.28)	213.31 (33.54)	238.05 (38.88)	0.468	
bcarot (mean (SD))		279.44 (175.71)	238.89 (155.00)	233.44 (106.12)	235.14 (143.08)	232.80 (130.83)	0.951	
vite (mean (SD))		7.95 (2.06)	7.87 (1.45)	8.18 (1.72)	8.07 (0.72)	9.05 (1.23)	0.448	
male (%)	Female	4 (44.4)	5 (50.0)	6 (66.7)	4 (50.0)	5 (50.0)	0.906	
	Male	5 (55.6)	5 (50.0)	3 (33.3)	4 (50.0)	5 (50.0)		

4.2 Time-Averaged Effect of Supplementation

The placebo group showed a negligible mean increase of 122 micro grams per mL, whereas the pooled active groups averaged an increase of 1,087 micro grams per ml an increase nearly nine times larger. Welch's test gave t = 6.65, df of about 9.3, p = $7.9 \times 10^{-}5$, and a 95% CI = (638, 1,291) (Shown in Appendix Table 8), showing a highly significant supplementation effect. Among the four active doses, ANOVA yielded F(3, 32) = 3.10, p = 0.040 (Shown in Appendix Table 9), indicating heterogeneity of mean delta. From this we can conclude supplementation with beta-carotene significantly increases the time-averaged serum beta-carotene level compared with no supplementation, and the magnitude of this depends on the dose as they are not all equal. Therefore, they are also dose dependent.

4.3 Longitudinal Trajectories and On and Off Treatment

4.3.1 On-treatment (months 4–9)

Table 2: LMM Fixed Effects (Treatment)

effect	term	estimate	std.error	statistic	df	p.value
fixed	(Intercept)	496.0232	207.39702	2.3916600	49.04542	0.0206514
fixed	month	-16.8692	22.55512	-0.7479099	86.57928	0.4565412
fixed	treatment	706.8024	231.39143	3.0545745	48.62010	0.0036517
fixed	month:treatment	34.3366	25.03853	1.3713502	84.38277	0.1739016

Table 3: LMM Fixed Effects (Dose)

effect	term	estimate	std.error	statistic	df	p.value
fixed	(Intercept)	602.317673	151.360967	3.9793461	43.72884	0.0002564
fixed	month	12.738939	17.083091	0.7457046	41.09168	0.4600906
fixed	dose	15.643623	4.152848	3.7669622	42.75761	0.0005003
fixed	month:dose	-0.075507	0.461350	-0.1636654	39.70074	0.8708250

Figure 1A shows that all dose groups track closely together through month 3, then diverge sharply once treatment begin at month 4. The curves remain roughly parallel through month 9 (Figure 1C). Table

2 summarizes fixed effects for the treatment model which showed a significant immediate effect, p-value = 0.0037, of supplementation with treated subjects having a 706.8 $\mu g/mL$ higher serum beta-carotene levels than placebo at treatment initiation. However, the time-trend interaction, month:treatment, was non-significant with a p-value of 0.1739, indicating no evidence that supplementation modifies serum beta-carotene levels over time. Similarly, on the dose dependent case in Table 3, we can see a similar result to the treatment model. The impact of beta-carotene supplementation is dose-dependent in terms of overall serum beta-carotene levels with a p-value < 0.001, but the effect of dose does not significantly alter the rate of change over time during the treatment period shown by the interaction term which has a p-value = 0.87. Thus, beta-carotene supplementation produces an immediate, dose dependent increase in serum beta-carotene, and that increase is maintained instead of increasing or decreasing over the six-month treatment period.

4.3.2 After Treatment (months 10–15)

Table 4: Quadratic Mixed Model with Dose Interactions (Post-Treatment Return)

effect	term	estimate	std.error	statistic	df	p.value
fixed	(Intercept)	1086.510	251.729	4.316	44.674	0.000
fixed	time_since_stop	-105.400	156.471	-0.674	153.224	0.502
fixed	dose	11.253	6.086	1.849	44.705	0.071
fixed	I(time_since_stop^2)	-16.912	29.989	-0.564	150.388	0.574
fixed	time_since_stop:dose	4.492	3.799	1.183	153.196	0.239
fixed	dose:I(time_since_stop^2)	-1.246	0.728	-1.711	150.287	0.089

Figure 1D shows that all supplemented groups fall toward baseline once treatments stop at month 10, and the decline curves remain nearly overlapping through month 15. Table 4 quantifies this pattern. The average linear drop after supplementation stopped was $105 \mu g/mL$ per month (95% CI -414, 203; p = 0.50) and the quadratic term was small and non-significant (p = 0.57), indicating no clear acceleration or deceleration overall. Although higher-dose subjects started the post supplementation phase slightly higher ($11.25 \mu g/mL$ per 1-mg increment, p = 0.07), neither the dose $\times$ time interaction (p = 0.24) nor the dose $\times$ $time^2$ interaction (p = 0.09) were statistically significant. Thus, once supplementation stops, all doses return toward baseline at similar rates. While dosage level shifts the starting beta-carotene level, it does not effect the return to baseline after supplementation (Appendix Figure 2).

4.4 Counter-factual Prediction under Continued Dosing

Table 5: Do covariates modify the treatment trajectory?

covariate	chisq	p_value
age_c	5.655	0.958
gender_m	23.934	0.032
bmi_c	12.100	0.519
chol_c	6.494	0.926

Adding each baseline covariate to the spline mixed-effects model as a time $\times$ treatment interaction yielded the likelihood-ratio results in Table 5. Age ($\chi^2 = 5.66$, p = 0.96), BMI ($\chi^2 = 12.10$, p = 0.52) and cholesterol ($\chi^2 = 6.49$, p = 0.93) did not improve model fit, indicating their trajectories under supplementation do

not vary from their reference groups. In contrast, gender altered the treatment curve ($\chi^2 = 23.93$, p = 0.032) with some statistical significance. The rise in serum beta-carotene during months 4–9 was steeper in men than in women, although both sexes returned toward baseline at comparable rates after month 10. Thus, among the covariates examined, only gender meaningfully modifies how beta-carotene levels evolve under supplementation; the effects of age, BMI, and cholesterol appear to not have an overall impact on beta-carotene levels.

4.5 Effect Modification and Secondary Findings

Based on the model fit in question 2 focusing on months 4-9, extending treatment from month 10 to month 12 would keep serum beta-carotene high and still creeping upward, with a clear dose-response pattern (Table 6). Within each patient the month-to-month gain was modest ($\approx$ 15–30 $\mu g/mL$), but across patients the predicted levels rose consistently with dose, demonstrating that continued supplementation would sustain and slightly amplify the dose-dependent elevations seen during the initial treatment phase. However, we can also notice a large amount of variability within each subject as looking at different ids within the same dosage group can have much greater differences.

Table 6: Predicted Beta-Carotene - Lower Doses

month	ID26 (0mg)	ID6 (0mg)	ID33 (15mg)	ID44 (15mg)	ID25 (30mg)
10	381.9	451.3	1049.5	1131.2	1601.0
11	406.7	469.9	1076.9	1132.0	1605.1
12	431.5	488.4	1104.4	1132.7	1609.2

Table 7: Predicted Beta-Carotene - Higher Doses

month	ID14 (30mg)	ID10 (45mg)	ID31 (45mg)	ID36 (60mg)	ID49 (60mg)
10	1241.8	1422.6	1101.6	1568.2	1731.5
11	1249.2	1433.5	1130.7	1568.7	1700.1
12	1256.6	1444.4	1159.8	1569.2	1668.7

5 Discussion

Our analyses show that oral beta-carotene supplementation produces a clear, dose-dependent rise in serum beta-carotene during the six-month treatment window and that, once treatments are stopped, concentrations decline toward baseline at a similar pace across doses. The magnitude of the time-averaged increase and the dose response showed a causal effect of supplementation. Post-treatment return to baseline, however, appears dose-independent. Effect-modification tests further indicate that age, BMI, and cholesterol do not alter treatment trajectories, whereas sex does. Longer term treatment predictions showed serum levels would have kept climbing modestly ($\approx$ 1–2% per month) and remained well separated by dose.

Some limitations hinder these conclusions. First, the sample was modest (n = 46) and some subjects had intermittent missing visits; although mixed-models borrow strength across individuals, sparse data may have reduced power to detect subtle interactions, especially in the analysis of the post supplementation phase. Additionally other confounders such as diet leave possible underlying factors not monitored.

Future studies should extend the follow-up period longer to confirm whether serum beta-carotene fully return to baseline. Also collecting dietary carotenoid intake looking into other confounders could help to emphasize the results. Possible oversampling of women and men separately to confirm the sex interraction would also help to answer that question more thoroughly.

6 Appendix

Figure 1. Beta-Carotene Levels Over Time

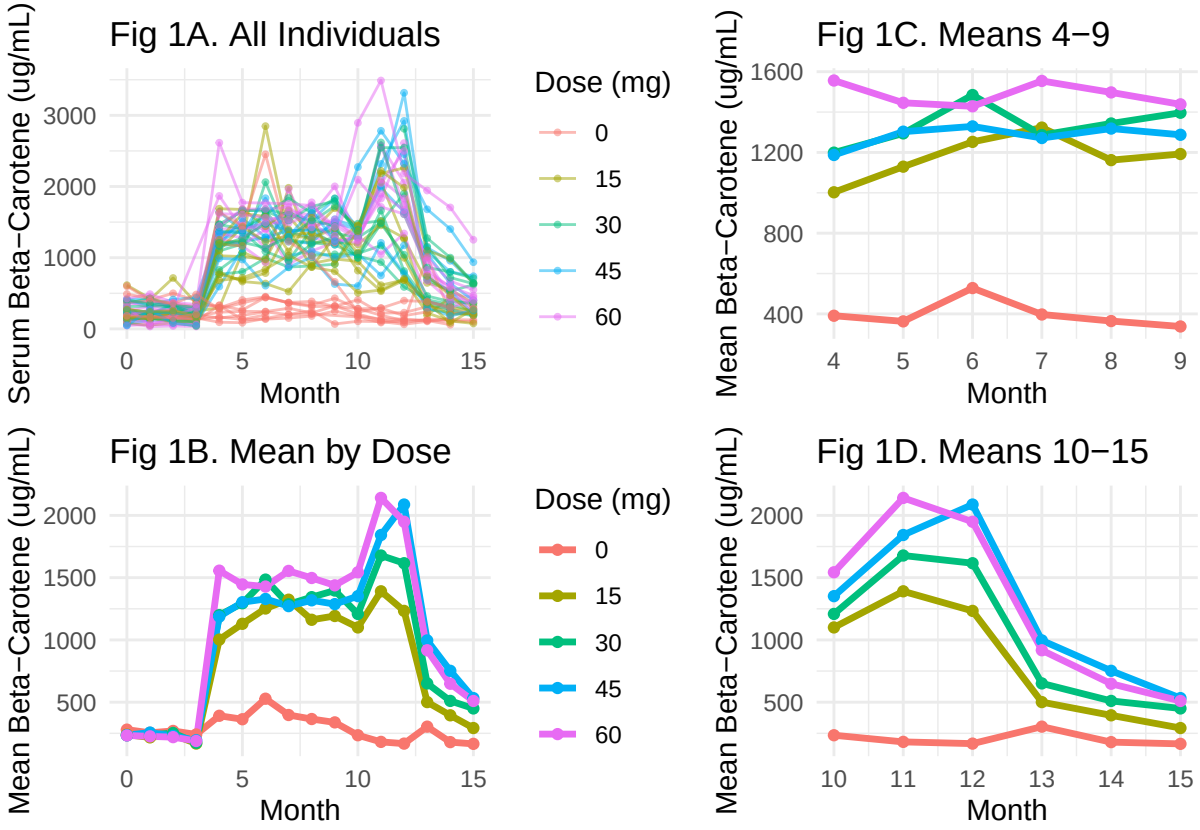


Table 8: Welch Two-Sample *t*-Test: Active vs Control

Mean (active)	Mean (control)	Difference	t	df	p.value	95% CI low	95% CI high
1086.909	122.3111	964.5981	6.645696	9.341146	7.919e-05	638.0733	1291.123

Table 9: One-Way ANOVA: Dose-Response Among Active Groups

Term	Df	Sum Sq	Mean Sq	F value	p-value
Dose	3	449995.9	149998.63	3.100815	4.040e-02
Residuals	32	1547966.0	48373.94	NA	NA

Figure 2 Quadratic Return To Baseline after Treatment Period

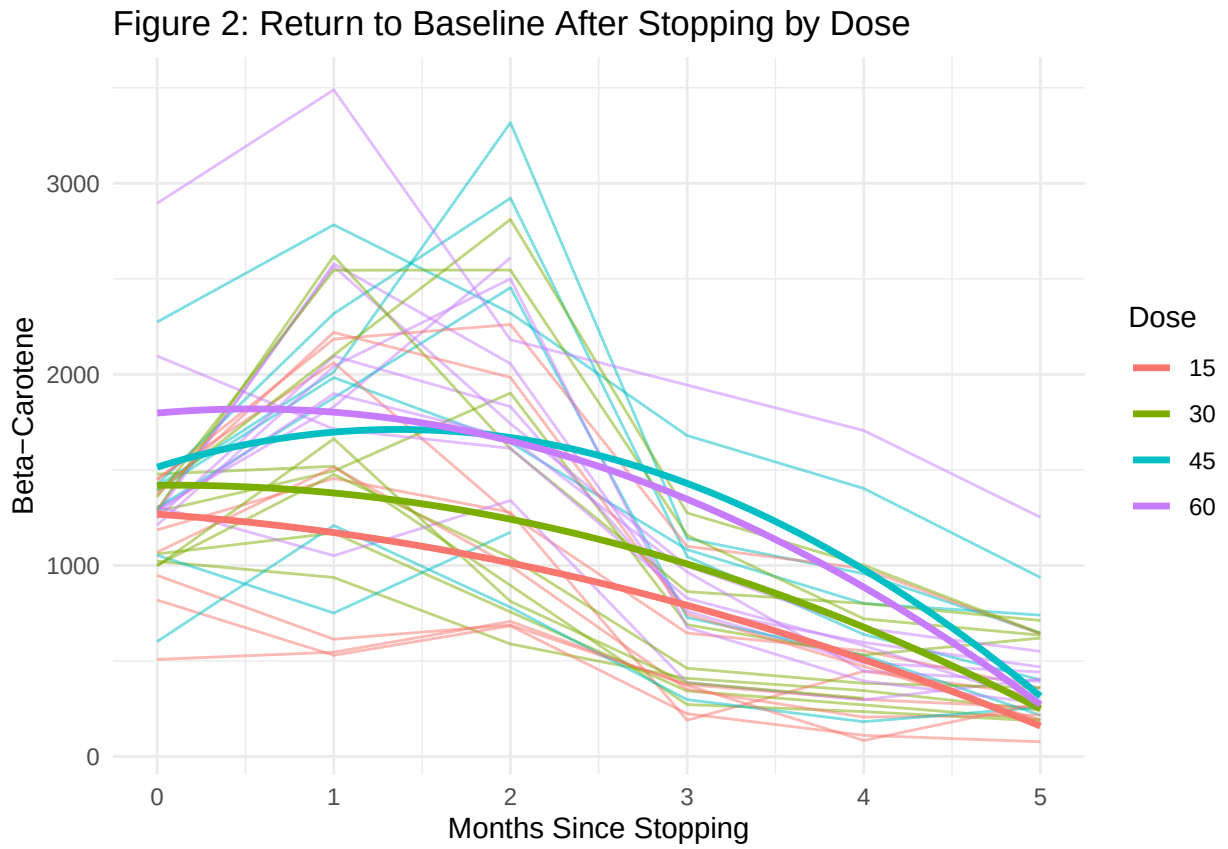


Figure 3: Covariates Split Beta-Carotene Levels Over Time

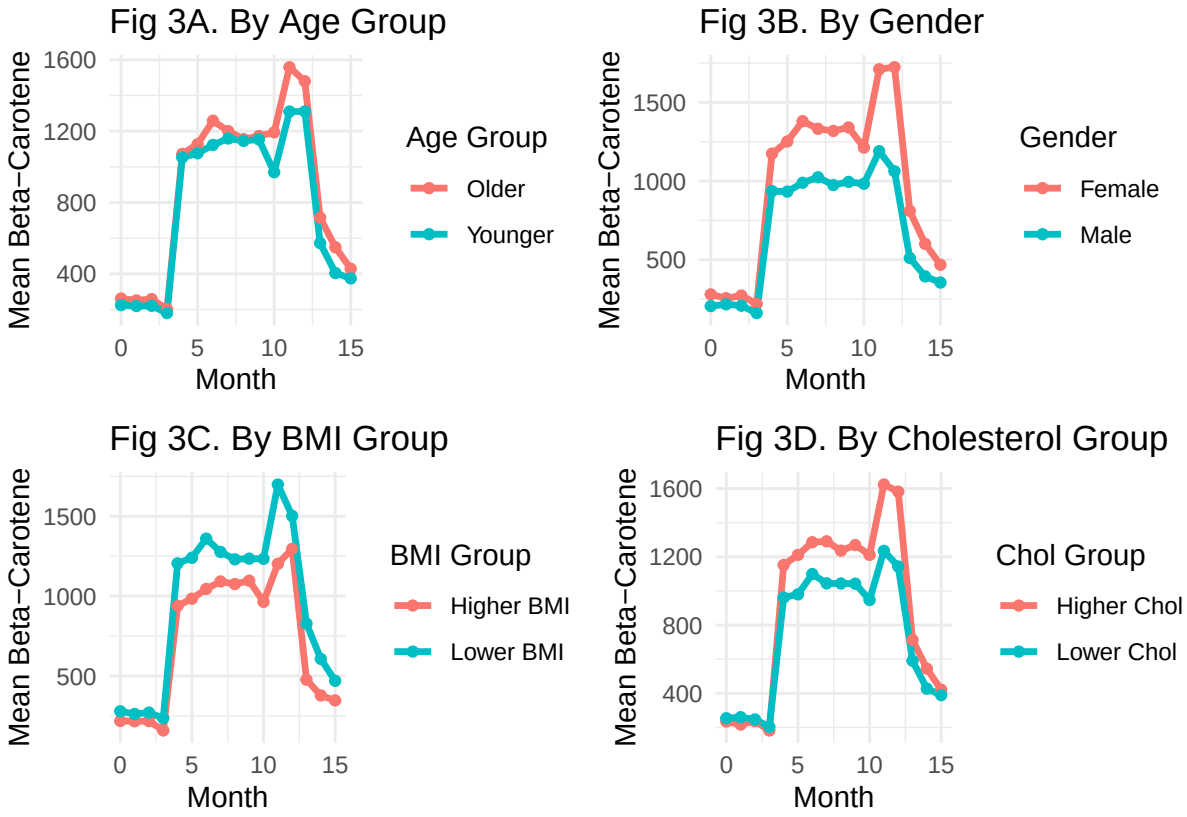


Figure 4: Observed vs Fitted Treatment Model (Question 2)

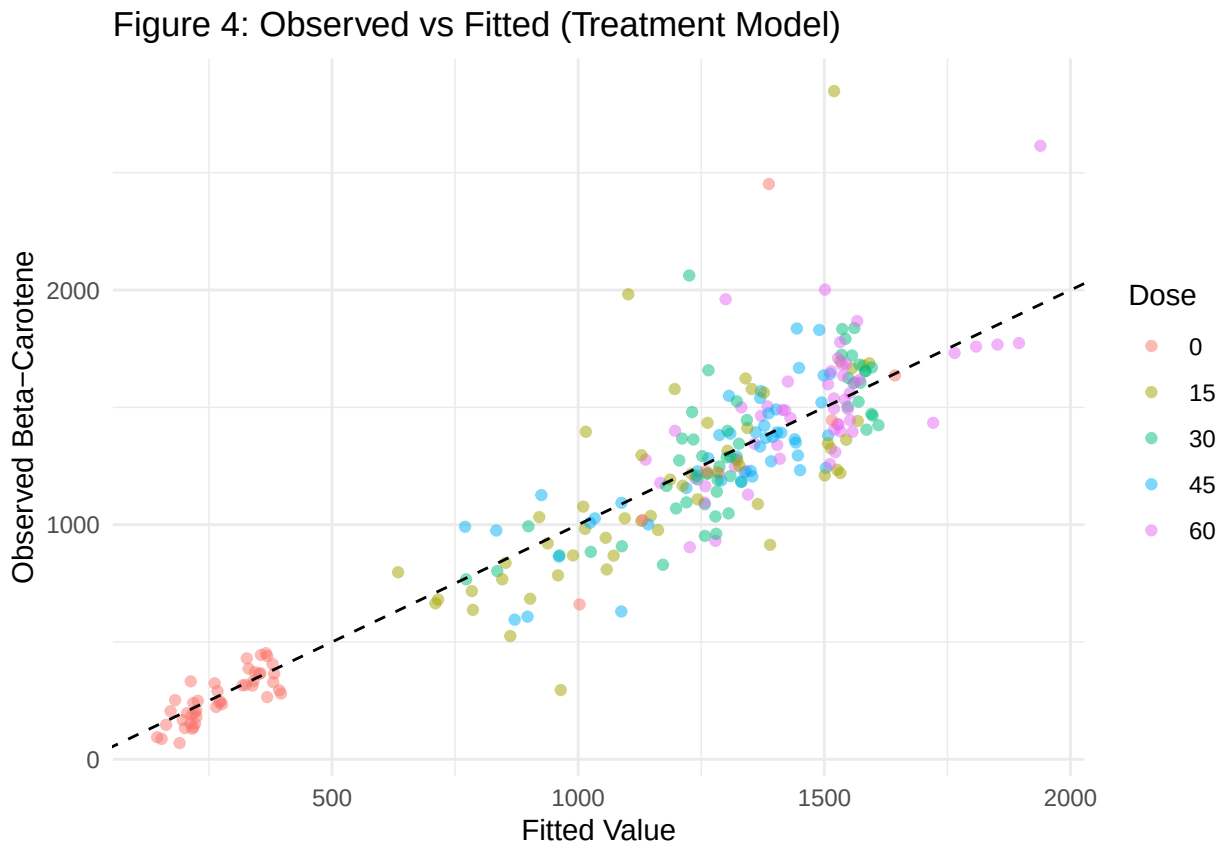


Figure 5: Missingness of Data

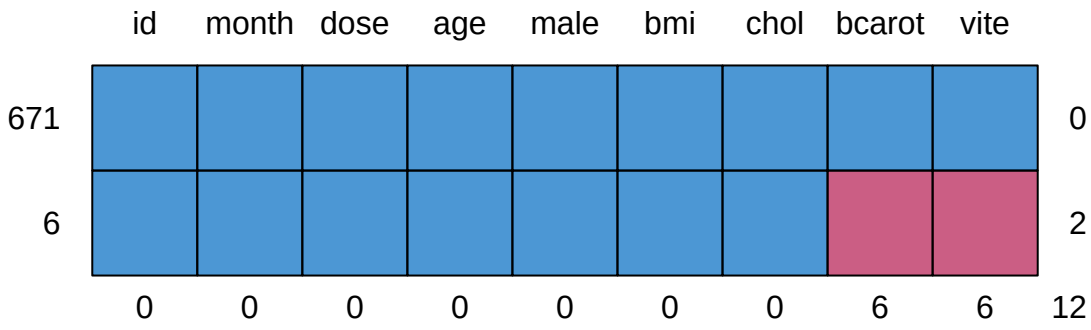
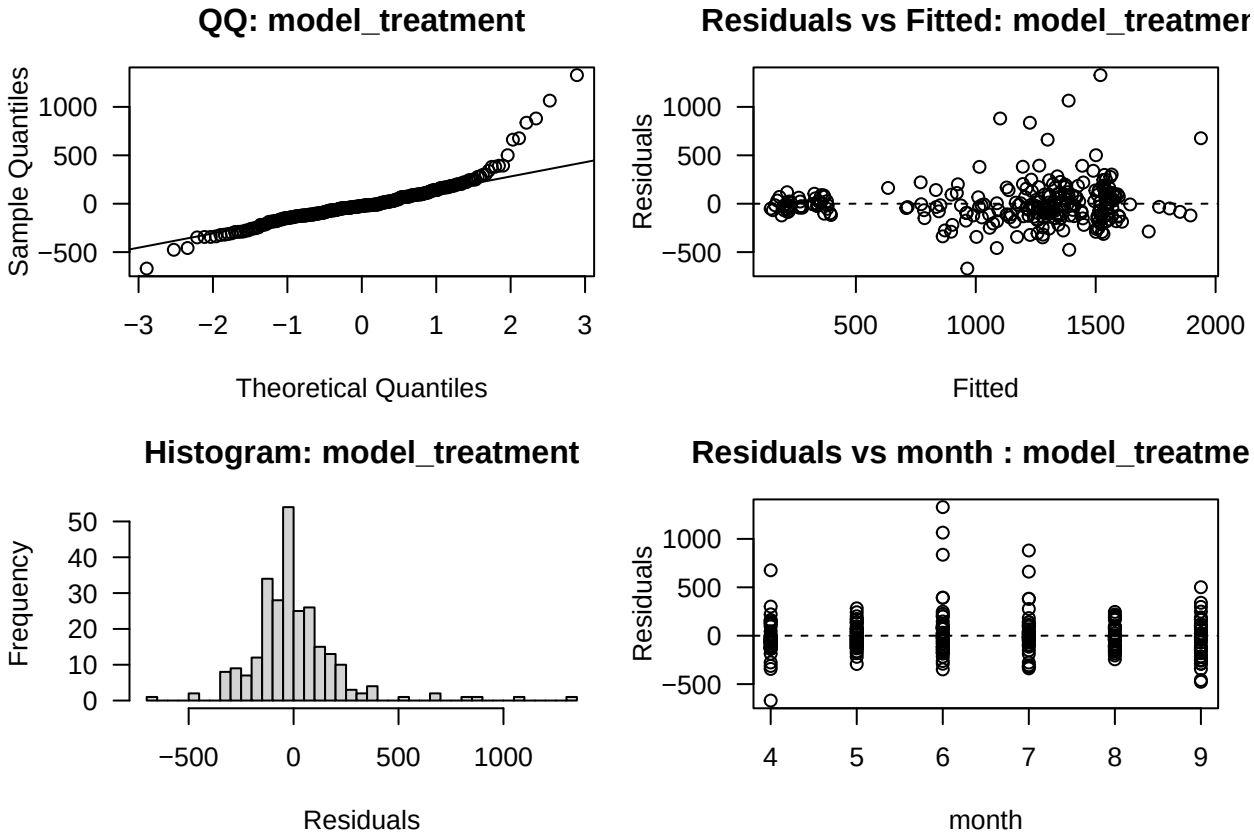
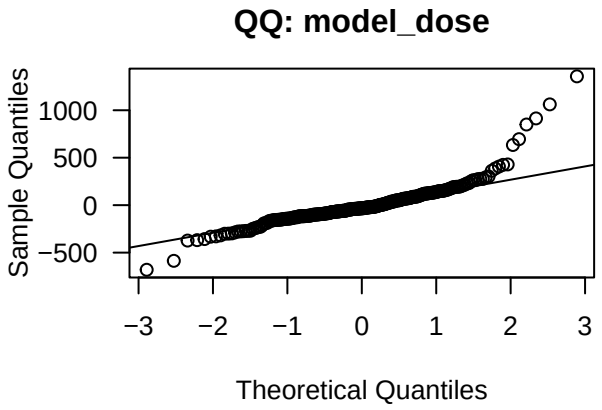


Figure 6: Model Diagnostics (Treatment, Dose, Quadratic)

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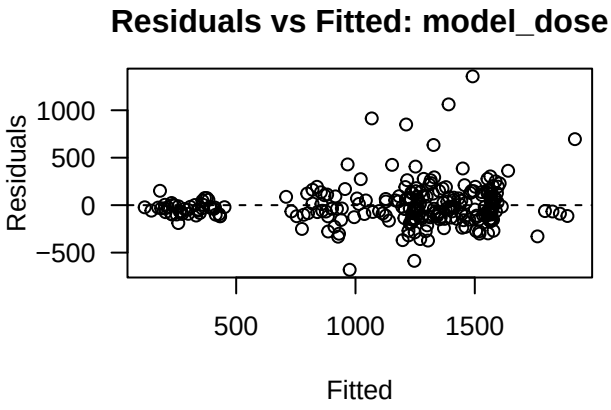
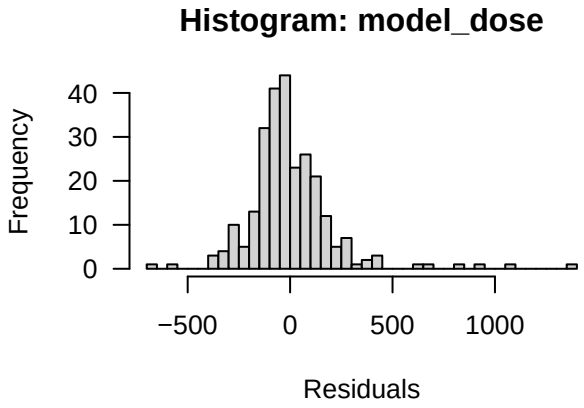
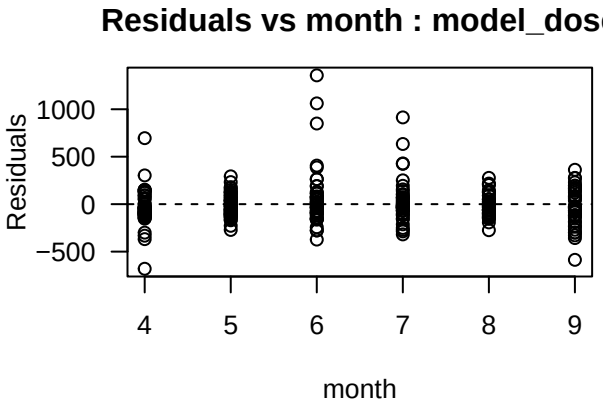
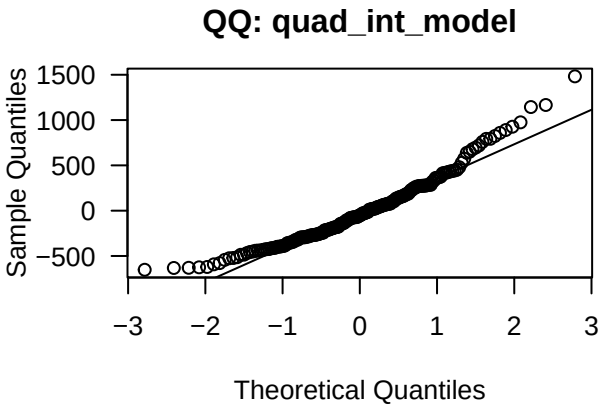
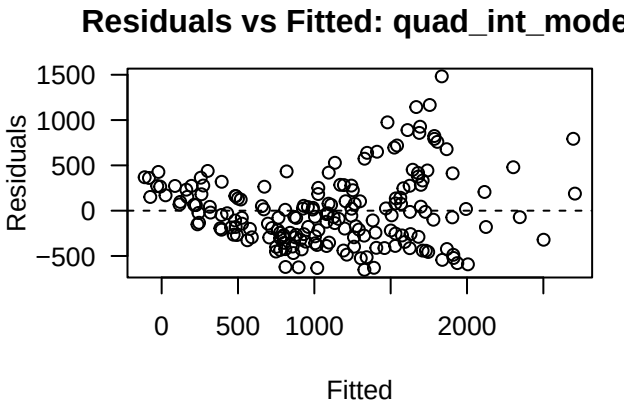
Sample Quantiles
1000
500
0
−500
−3
−2
−1
0
1
2
3
Theoretical Quantiles

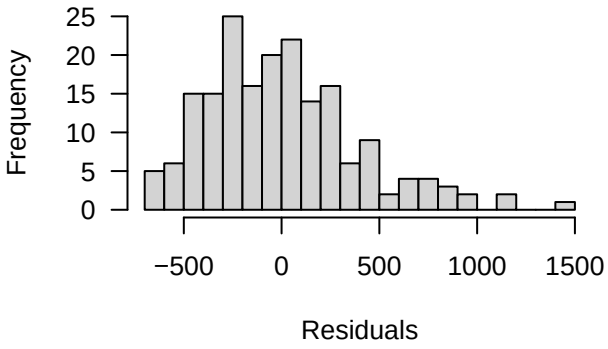

Residuals vs Fitted: model_dose
Residuals
1000
500
0
−500
500
1000
1500
Fitted

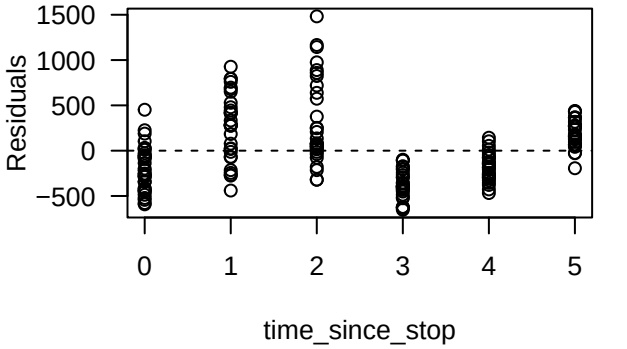

Histogram: model_dose
Frequency
40
30
20
10
0
−500
0
500
1000
Residuals


Residuals vs month : model_dose
Residuals
1000
500
0
−500
4
5
6
7
8
9
month


QQ: quad_int_model
Sample Quantiles
Theoretical Quantiles
1500
1000
500
0
−500
−3
−2
−1
0
1
2
3


Residuals vs Fitted: quad_int_mode
Residuals
Fitted
1500
1000
500
0
−500
0
500
1000
2000


Histogram: quad_int_model
Frequency
Residuals
25
20
15
10
5
0
−500
0
500
1000
1500


Residuals vs time_since_stop : quad_int_
Residuals
time_since_stop
1500
1000
500
0
−500
0
1
2
3
4
5

7 References

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