Glutathione ratios as the mechanism of action of lipoic acid in progressive multiple sclerosis (PI: Rebecca Spain)

Benjamin Chan (chanb@ohsu.edu)

2018-06-13

# Import raw data

Joined data set. Include only the

* Study design variables,
* Normalized concentrations, and
* GSH/GSSG ratios

## Clean data

Data check **before cleaning**.

|  |  |  |  |
| --- | --- | --- | --- |
| patientID | hasM0 | hasM3 | hasM12 |
| 120 | 1 | 0 | 1 |
| 122 | 1 | 0 | 1 |
| 134 | 1 | 1 | 2 |
| 143 | 0 | 2 | 0 |

Recode data per Cassidy’s email

From: Cassidy Taylor  
Sent: Monday, March 12, 2018 3:17 PM  
To: Benjamin Chan [chanb@ohsu.edu](mailto:chanb@ohsu.edu); Rebecca Spain [spainr@ohsu.edu](mailto:spainr@ohsu.edu)  
Subject: RE: Rebecca Spain Glutathione Study

Just heard back from the lab and based on the remaining levels of blood, the manifest was incorrectly labeled. It should read

Sample 44 = 143 M0  
Sample 45 = 143 M3  
Sample 46 = 143 M12

From: Carin Waslo  
Sent: Wednesday, June 13, 2018 10:27 AM  
To: Benjamin Chan [chanb@ohsu.edu](mailto:chanb@ohsu.edu)  
Cc: Rebecca Spain [spainr@ohsu.edu](mailto:spainr@ohsu.edu); Cassidy Taylor [taylocas@ohsu.edu](mailto:taylocas@ohsu.edu)  
Subject: SECURE: Spain - Glutathione ratios as the mechanism of action of LA in PMS

Good morning,

I work for Dr. Rebecca Spain and have been given the opportunity to develop a poster for the Glutathione ratios as the mechanism of action of lipoic acid in PMS study. While looking through the results, I noted an error in study arm assignment for PatientID #123. PatientID #123 is listed as having received Placebo, but actually had received LA.

Could you please assign PatientID #123 to the LA study arm and rerun the analysis? This should make each study arm contain 10 subjects. I am sorry for any inconvenience.

Data check **after cleaning**. Should return a data frame with only patientID %in% c(120, 122).

|  |  |  |  |
| --- | --- | --- | --- |
| patientID | hasM0 | hasM3 | hasM12 |
| 120 | 1 | 0 | 1 |
| 122 | 1 | 0 | 1 |

## Create analytic data frames for each aim

Aim 1

## Classes 'tbl\_df', 'tbl' and 'data.frame': 58 obs. of 9 variables:  
## $ sampleID : num 1 2 3 4 5 6 7 8 9 10 ...  
## $ patientID : Factor w/ 20 levels "118","119","120",..: 1 1 1 2 2 2 3 3 4 4 ...  
## $ visitMonth : Factor w/ 3 levels "0","3","12": 1 2 3 1 2 3 1 3 1 3 ...  
## $ studyArm : Factor w/ 2 levels "LA","Placebo": 1 1 1 2 2 2 2 2 2 2 ...  
## $ normalizedConcGSH : num 125 101 137 87 171 ...  
## $ normalizedConcGSSG : num 0.931 0.639 0.828 0.693 1.291 ...  
## $ normalizedConcStdEGSH : num 2.287 2.06 0.0847 0.3121 1.1748 ...  
## $ normalizedConcStdEGSSG: num 0.223 0.17 0.229 0.186 0.352 ...  
## $ normalizedConcRatio : num 134 158 166 126 132 ...

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| patientID | visitMonth | studyArm | normalizedConcGSH | normalizedConcGSSG | normalizedConcRatio |
| 118 | 0 | LA | 125.06 | 0.93 | 134.39 |
| 118 | 3 | LA | 100.76 | 0.64 | 157.79 |
| 118 | 12 | LA | 137.35 | 0.83 | 165.82 |
| 123 | 0 | LA | 96.34 | 0.63 | 152.45 |
| 123 | 3 | LA | 131.28 | 1.00 | 131.92 |
| 123 | 12 | LA | 110.30 | 0.86 | 128.95 |
| 124 | 0 | LA | 127.61 | 0.76 | 168.90 |
| 124 | 3 | LA | 86.82 | 0.51 | 169.44 |
| 124 | 12 | LA | 109.10 | 0.64 | 171.58 |
| 129 | 0 | LA | 175.84 | 1.03 | 171.36 |
| 129 | 3 | LA | 134.91 | 0.96 | 140.36 |
| 129 | 12 | LA | 120.29 | 0.69 | 175.25 |
| 130 | 0 | LA | 102.18 | 0.69 | 148.02 |
| 130 | 3 | LA | 142.32 | 0.94 | 151.86 |
| 130 | 12 | LA | 170.98 | 0.97 | 176.26 |
| 132 | 0 | LA | 164.86 | 1.18 | 139.21 |
| 132 | 3 | LA | 159.88 | 0.95 | 168.87 |
| 132 | 12 | LA | 156.80 | 0.95 | 165.67 |
| 134 | 0 | LA | 121.36 | 0.86 | 140.53 |
| 134 | 3 | LA | 117.52 | 0.68 | 173.03 |
| 134 | 12 | LA | 166.19 | 0.94 | 176.27 |
| 140 | 0 | LA | 135.54 | 0.82 | 166.15 |
| 140 | 3 | LA | 123.01 | 0.81 | 152.21 |
| 140 | 12 | LA | 145.25 | 0.99 | 147.36 |
| 149 | 0 | LA | 111.48 | 0.71 | 157.75 |
| 149 | 3 | LA | 120.45 | 0.84 | 143.15 |
| 149 | 12 | LA | 133.68 | 0.83 | 160.44 |
| 151 | 0 | LA | 101.74 | 0.60 | 170.28 |
| 151 | 3 | LA | 92.33 | 0.58 | 160.44 |
| 151 | 12 | LA | 108.97 | 0.66 | 166.27 |
| 119 | 0 | Placebo | 86.95 | 0.69 | 125.56 |
| 119 | 3 | Placebo | 171.00 | 1.29 | 132.47 |
| 119 | 12 | Placebo | 185.79 | 1.42 | 131.09 |
| 120 | 0 | Placebo | 108.99 | 0.81 | 134.69 |
| 120 | 12 | Placebo | 144.20 | 1.00 | 143.82 |
| 122 | 0 | Placebo | 124.43 | 0.97 | 127.89 |
| 122 | 12 | Placebo | 126.22 | 0.94 | 134.53 |
| 125 | 0 | Placebo | 93.27 | 0.74 | 126.19 |
| 125 | 3 | Placebo | 91.82 | 0.64 | 143.24 |
| 125 | 12 | Placebo | 116.12 | 0.90 | 128.79 |
| 131 | 0 | Placebo | 183.91 | 1.47 | 124.82 |
| 131 | 3 | Placebo | 129.58 | 1.02 | 126.79 |
| 131 | 12 | Placebo | 116.74 | 0.93 | 125.19 |
| 135 | 0 | Placebo | 109.98 | 0.71 | 155.24 |
| 135 | 3 | Placebo | 133.95 | 0.83 | 160.95 |
| 135 | 12 | Placebo | 143.38 | 0.97 | 148.21 |
| 139 | 0 | Placebo | 162.97 | 1.16 | 140.65 |
| 139 | 3 | Placebo | 156.30 | 1.14 | 137.41 |
| 139 | 12 | Placebo | 161.13 | 1.14 | 141.52 |
| 143 | 0 | Placebo | 143.55 | 1.14 | 125.84 |
| 143 | 3 | Placebo | 169.13 | 1.33 | 127.29 |
| 143 | 12 | Placebo | 97.65 | 0.55 | 176.13 |
| 145 | 0 | Placebo | 110.28 | 0.90 | 122.08 |
| 145 | 3 | Placebo | 97.01 | 0.78 | 123.97 |
| 145 | 12 | Placebo | 109.46 | 0.83 | 132.14 |
| 153 | 0 | Placebo | 100.72 | 0.69 | 146.84 |
| 153 | 3 | Placebo | 93.73 | 0.77 | 121.86 |
| 153 | 12 | Placebo | 96.02 | 0.80 | 120.52 |

Aim 2

## Classes 'tbl\_df', 'tbl' and 'data.frame': 20 obs. of 8 variables:  
## $ patientID : Factor w/ 20 levels "118","119","120",..: 1 2 3 4 5 6 7 8 9 10 ...  
## $ studyArm : Factor w/ 2 levels "LA","Placebo": 1 2 2 2 1 1 2 1 1 2 ...  
## $ concRatioM0 : num 134 126 135 128 152 ...  
## $ concRatioM12 : num 166 131 144 135 129 ...  
## $ pctChangeConcRatio : num 23.39 4.4 6.78 5.2 -15.41 ...  
## $ brainAtrophy : num 0.358 -2.026 -1.544 0.534 -0.679 ...  
## $ wholeBrainVol : num 1389025 1437526 1385963 1393046 1413702 ...  
## $ wholeBrainVolScaled: num [1:20, 1] -0.652 0.142 -0.702 -0.586 -0.248 ...  
## ..- attr(\*, "scaled:center")= num 1428831  
## ..- attr(\*, "scaled:scale")= num 61028

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| patientID | studyArm | concRatioM0 | concRatioM12 | pctChangeConcRatio | brainAtrophy | wholeBrainVol | wholeBrainVolScaled |
| 118 | LA | 134.39 | 165.82 | 23.39 | 0.36 | 1389025 | -0.65225435 |
| 123 | LA | 152.45 | 128.95 | -15.41 | -0.68 | 1413702 | -0.24790021 |
| 124 | LA | 168.90 | 171.58 | 1.59 | 0.80 | 1403817 | -0.40987661 |
| 129 | LA | 171.36 | 175.25 | 2.27 | -1.46 | 1394722 | -0.55890808 |
| 130 | LA | 148.02 | 176.26 | 19.08 | 0.20 | 1465597 | 0.60244636 |
| 132 | LA | 139.21 | 165.67 | 19.01 | -1.55 | 1442353 | 0.22157254 |
| 134 | LA | 140.53 | 176.27 | 25.44 | 0.60 | 1494836 | 1.08157144 |
| 140 | LA | 166.15 | 147.36 | -11.31 | -1.11 | 1432413 | 0.05869458 |
| 149 | LA | 157.75 | 160.44 | 1.71 | 0.07 | 1548241 | 1.95665694 |
| 151 | LA | 170.28 | 166.27 | -2.36 | -0.16 | 1463387 | 0.56623855 |
| 119 | Placebo | 125.56 | 131.09 | 4.40 | -2.03 | 1437526 | 0.14247847 |
| 120 | Placebo | 134.69 | 143.82 | 6.78 | -1.54 | 1385963 | -0.70243336 |
| 122 | Placebo | 127.89 | 134.53 | 5.20 | 0.53 | 1393046 | -0.58637150 |
| 125 | Placebo | 126.19 | 128.79 | 2.06 | -1.12 | 1398976 | -0.48919566 |
| 131 | Placebo | 124.82 | 125.19 | 0.29 | -1.75 | 1583152 | 2.52871095 |
| 135 | Placebo | 155.24 | 148.21 | -4.52 | -0.27 | 1460338 | 0.51628125 |
| 139 | Placebo | 140.65 | 141.52 | 0.62 | -2.17 | 1393658 | -0.57634163 |
| 143 | Placebo | 125.84 | 176.13 | 39.96 | -1.74 | 1339494 | -1.46386607 |
| 145 | Placebo | 122.08 | 132.14 | 8.25 | -2.01 | 1355211 | -1.20633292 |
| 153 | Placebo | 146.84 | 120.52 | -17.93 | -1.22 | 1381158 | -0.78117069 |

# Aim 1

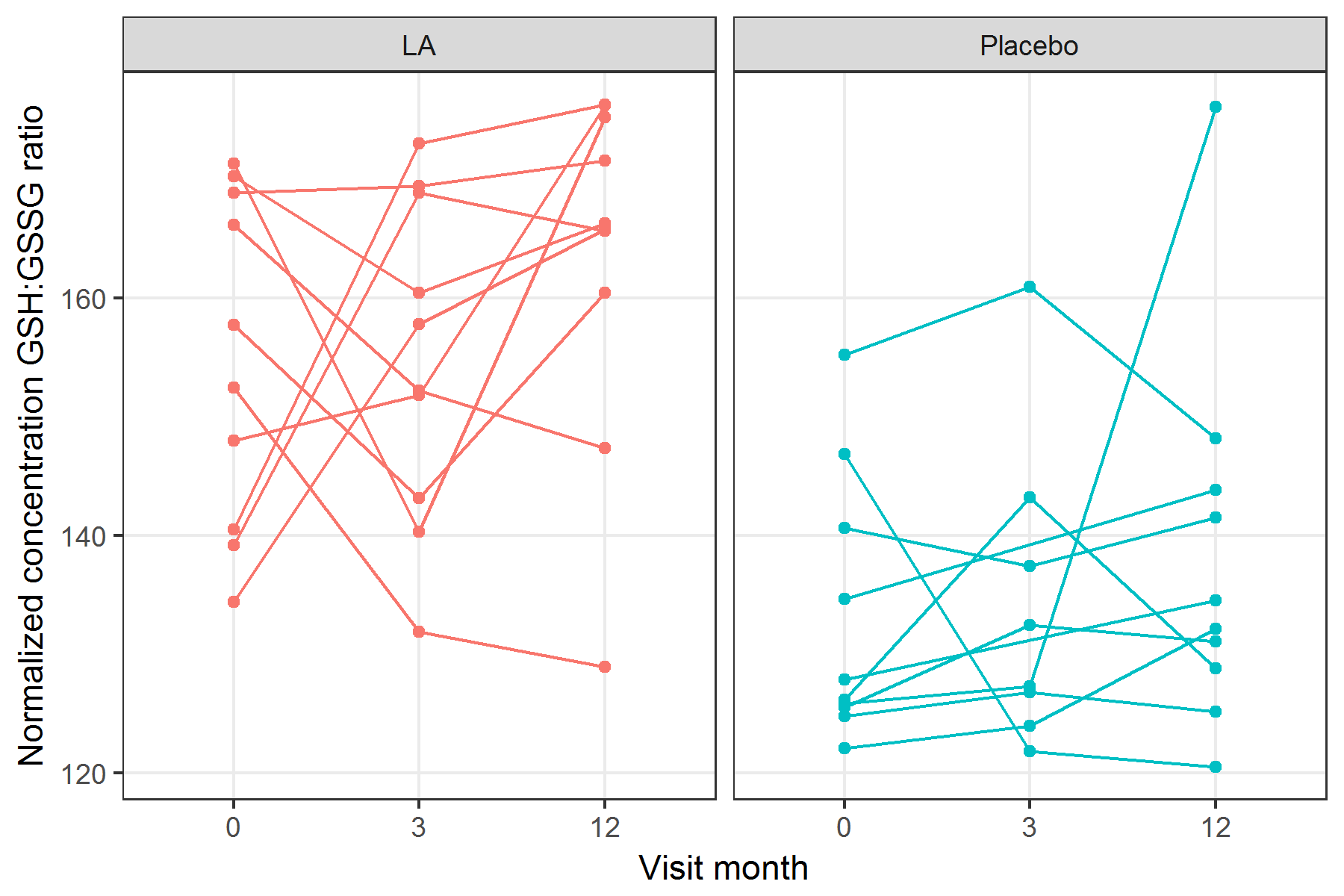
The model for Aim 1 will be a random intercept linear model. Estimation will use the *lme4* package.

##   
## To cite lme4 in publications use:  
##   
## Douglas Bates, Martin Maechler, Ben Bolker, Steve Walker (2015).  
## Fitting Linear Mixed-Effects Models Using lme4. Journal of  
## Statistical Software, 67(1), 1-48. doi:10.18637/jss.v067.i01.  
##   
## A BibTeX entry for LaTeX users is  
##   
## @Article{,  
## title = {Fitting Linear Mixed-Effects Models Using {lme4}},  
## author = {Douglas Bates and Martin M{\"a}chler and Ben Bolker and Steve Walker},  
## journal = {Journal of Statistical Software},  
## year = {2015},  
## volume = {67},  
## number = {1},  
## pages = {1--48},  
## doi = {10.18637/jss.v067.i01},  
## }

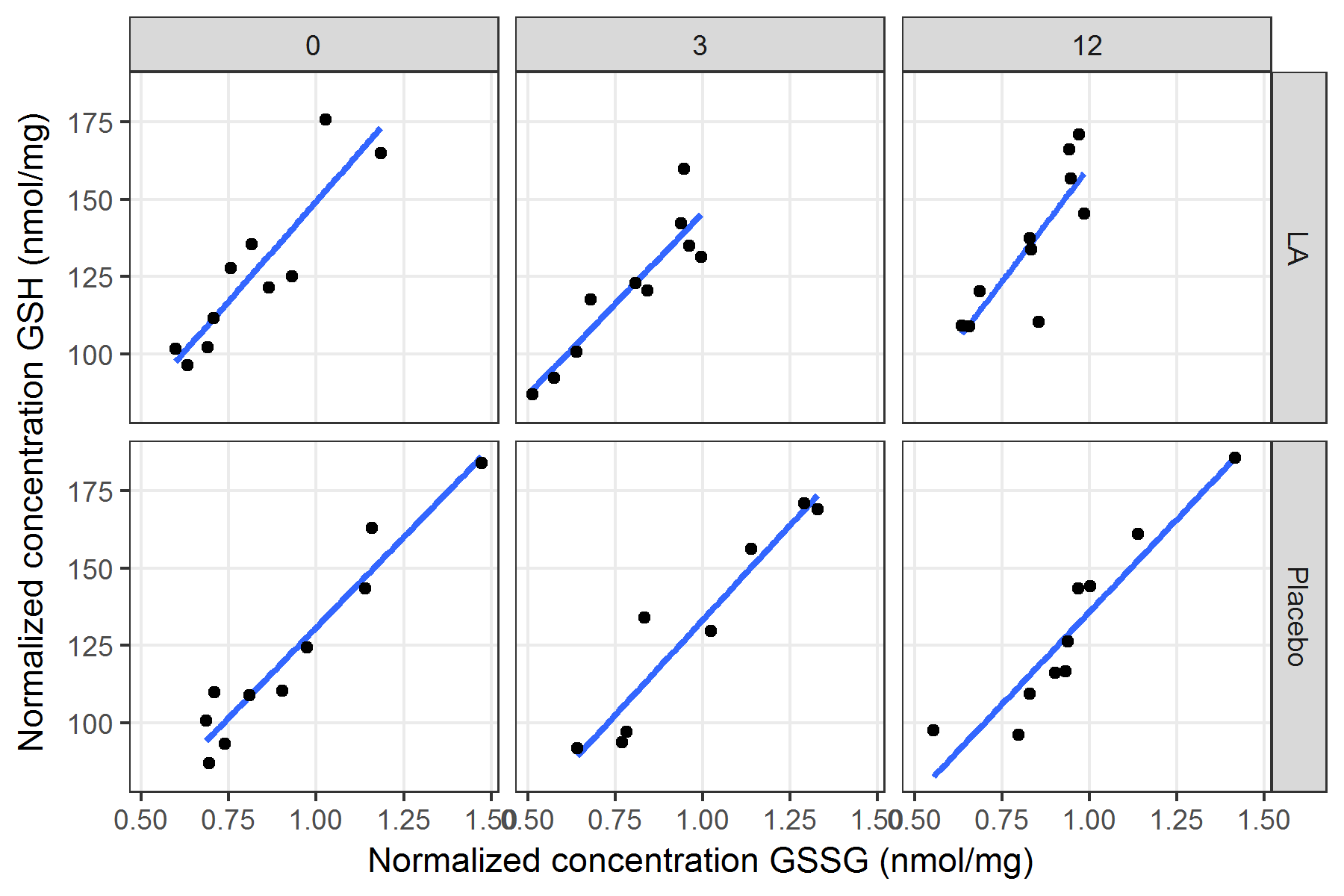
The model is

where is the random intercept component for each study subject , and is the random error.

## Normalized GSH:GSSG concentration ratio



figures/lineplotNormalizedConcRatio.png



figures/plotNormalizedConcSlope.png

Mixed effects model using the **lme4** package.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| term | estimate | std.error | statistic | df | pvalue |
| (Intercept) | 154.90 | 4.38 | 35.38 | 34 | 0.0000 |
| studyArmPlacebo | -21.92 | 6.19 | -3.54 | 18 | 0.0023 |
| visitMonth3 | 0.00 | 5.73 | 0.00 | 34 | 0.9995 |
| visitMonth12 | 8.48 | 5.73 | 1.48 | 34 | 0.1478 |
| studyArmPlacebo:visitMonth3 | 1.24 | 8.38 | 0.15 | 34 | 0.8830 |
| studyArmPlacebo:visitMonth12 | -3.27 | 8.10 | -0.40 | 34 | 0.6891 |

## Note: uncertainty of the random effects parameters are not taken into account for confidence intervals.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| group | x | predicted | conf.low | conf.high |
| LA | 0 | 154.9033 | 146.3226 | 163.4839 |
| LA | 3 | 154.9072 | 146.3266 | 163.4879 |
| LA | 12 | 163.3880 | 154.8073 | 171.9686 |
| Placebo | 0 | 132.9788 | 124.3982 | 141.5595 |
| Placebo | 3 | 134.2257 | 125.6450 | 142.8063 |
| Placebo | 12 | 138.1935 | 129.6128 | 146.7741 |

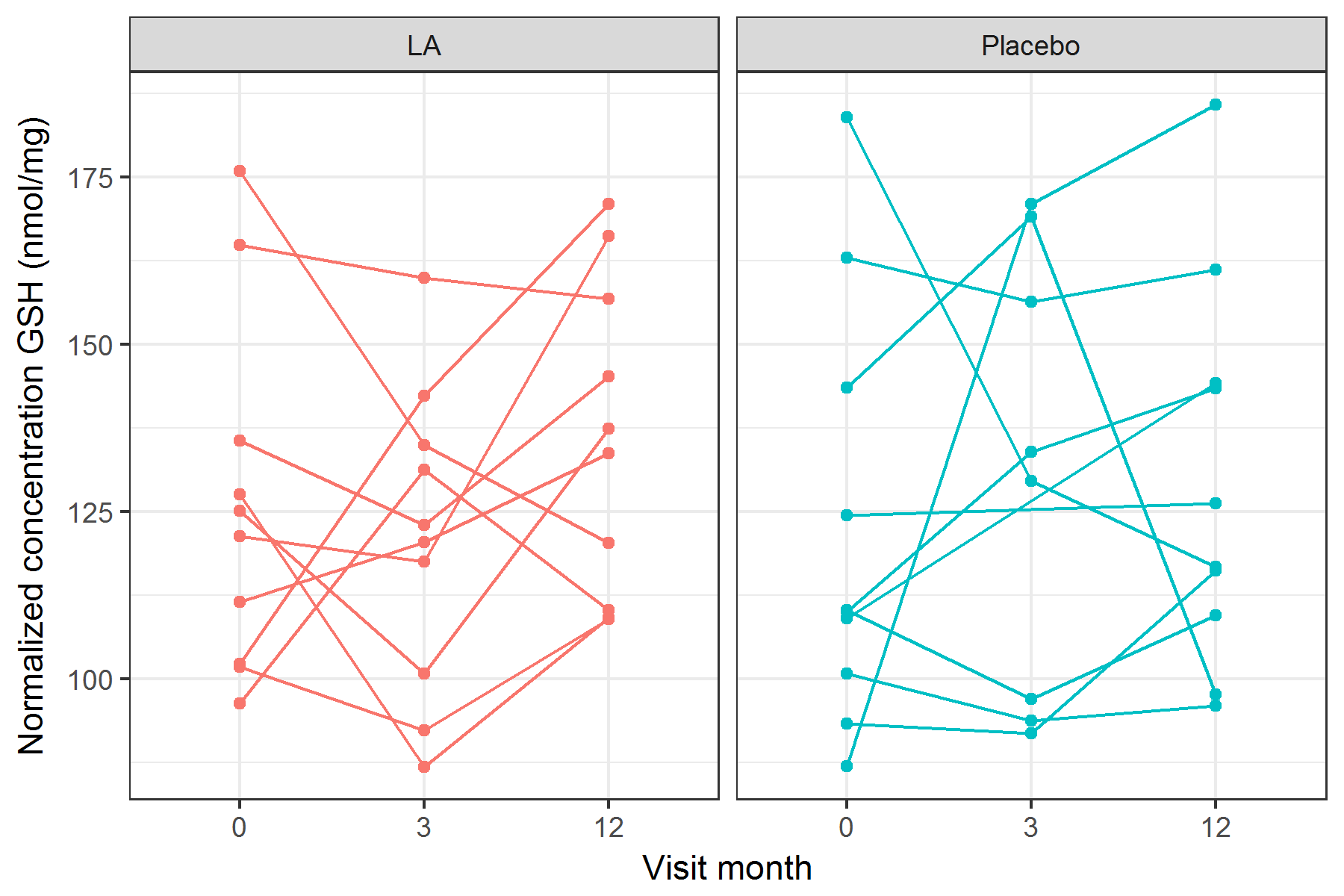
## Note: uncertainty of the random effects parameters are not taken into account for confidence intervals.

Details (not shown).

Mixed effects model using the **nlme** package.

*Not executed.* The lme4::lmer() function is good enough.

## Normalized concentration GSH



figures/lineplotNormalizedConcGSH.png

Mixed effects model using the **lme4** package.

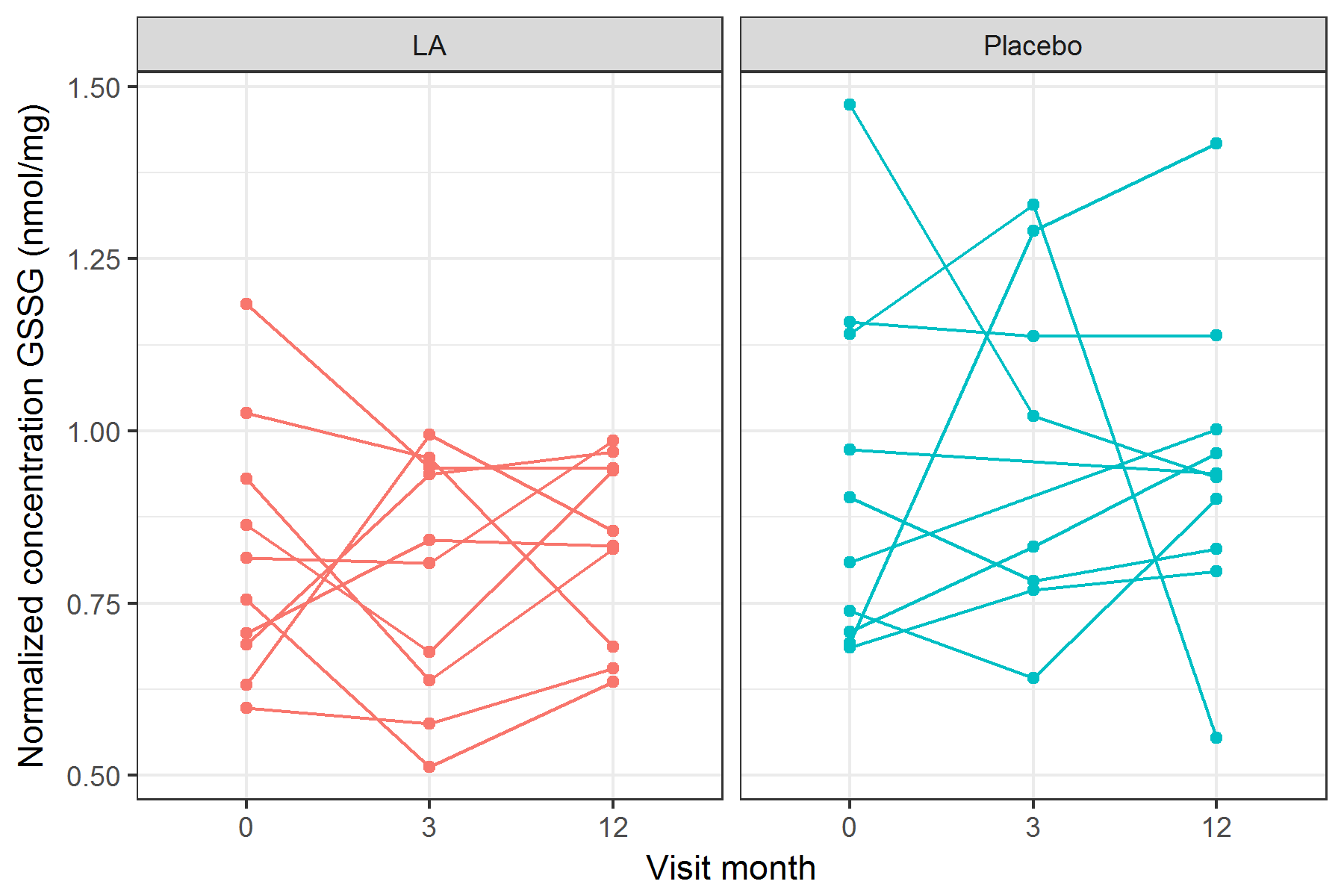
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| term | estimate | std.error | statistic | df | pvalue |
| (Intercept) | 126.20 | 8.78 | 14.38 | 34 | 0.0000 |
| studyArmPlacebo | -3.69 | 12.41 | -0.30 | 18 | 0.7694 |
| visitMonth3 | -5.27 | 10.63 | -0.50 | 34 | 0.6230 |
| visitMonth12 | 9.69 | 10.63 | 0.91 | 34 | 0.3685 |
| studyArmPlacebo:visitMonth3 | 13.07 | 15.59 | 0.84 | 34 | 0.4077 |
| studyArmPlacebo:visitMonth12 | -2.52 | 15.03 | -0.17 | 34 | 0.8676 |

Details (not shown).

Mixed effects model using the **nlme** package.

*Not executed.* The lme4::lmer() function is good enough.

## Normalized concentration GSSG



figures/lineplotNormalizedConcGSSG.png

Mixed effects model using the **lme4** package.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| term | estimate | std.error | statistic | df | pvalue |
| (Intercept) | 0.82 | 0.07 | 12.41 | 34 | 0.0000 |
| studyArmPlacebo | 0.11 | 0.09 | 1.16 | 18 | 0.2621 |
| visitMonth3 | -0.03 | 0.08 | -0.36 | 34 | 0.7196 |
| visitMonth12 | 0.01 | 0.08 | 0.16 | 34 | 0.8726 |
| studyArmPlacebo:visitMonth3 | 0.08 | 0.12 | 0.62 | 34 | 0.5383 |
| studyArmPlacebo:visitMonth12 | 0.01 | 0.12 | 0.05 | 34 | 0.9629 |

Details (not shown).

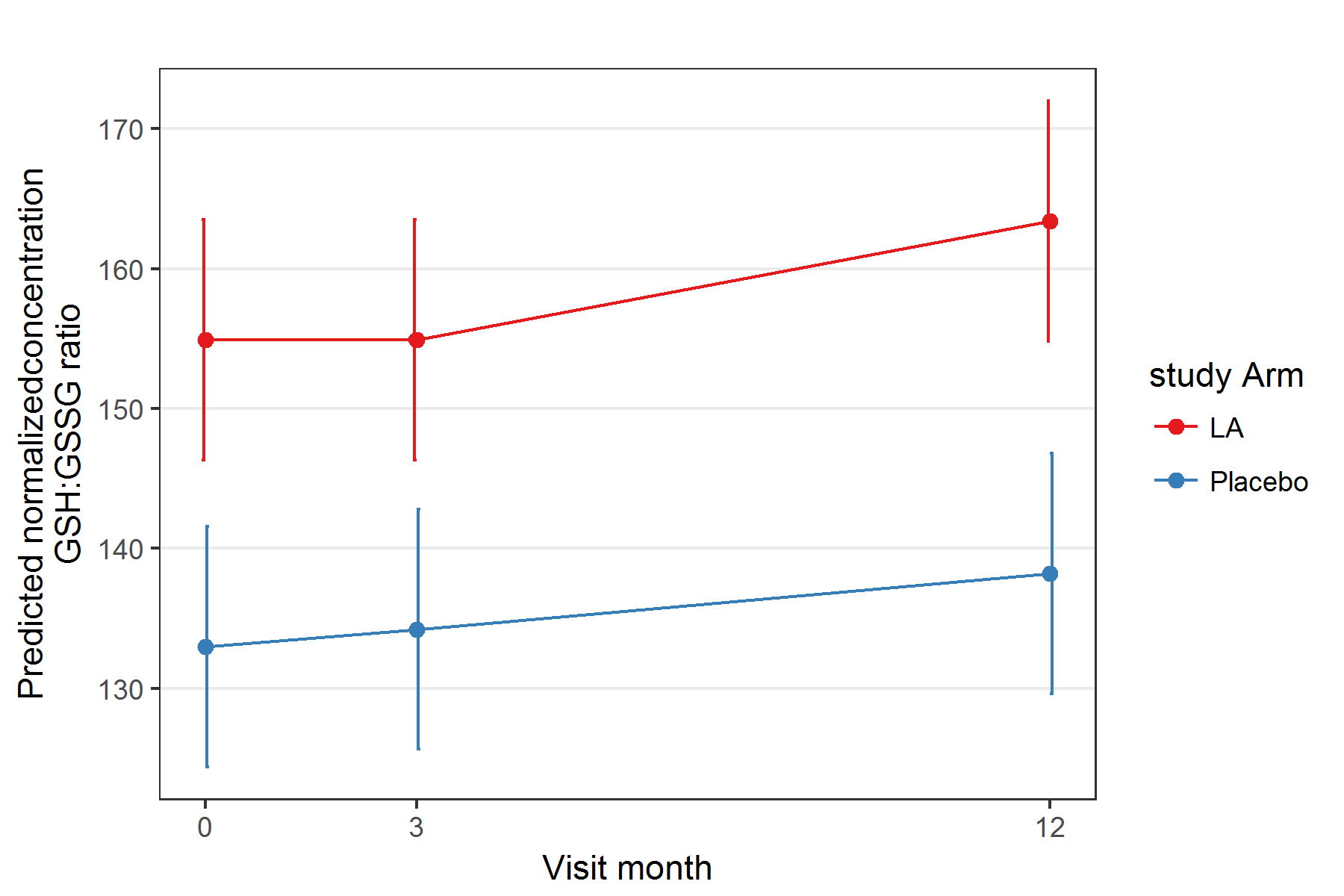
Mixed effects model using the **nlme** package.

*Not executed.* The lme4::lmer() function is good enough.

## Interpretation

### Normalized concentration ratio

* Normalized concentration ratio was significantly different between placebo and LA
  + Difference between placebo and LA at baseline visit was -21.9 (p-value = 0.0023)
  + Difference between placebo and LA at 3-month visit was -20.7 (p-value = 0.0055)
  + Difference between placebo and LA at 12-month visit was -25.2 (p-value = 7.2 × 10-4)
  + Difference between placebo and LA at baseline visit was not significantly different compared to month 3 or month 12 visits (i.e., difference between placebo and LA was significant at **all visits**)
  + Global difference between placebo and LA was -22.5 (p-value = 3.3 × 10-5)
* Normalized concentration ratio was not significantly different between visits, either within the placebo group or LA group
  + Among LA: difference between 3-month visit and baseline was 0.00397 (p-value = 1)
  + Among LA: difference between 12-month visit and baseline was 8.48 (p-value = 0.15)
  + Among placebo: difference between 3-month visit and baseline was 1.25 (p-value = 0.84)
  + Among placebo: difference between 12-month visit and baseline was 5.21 (p-value = 0.37)
* The differences in normalized concentration ratio from baseline were not significantly different between LA and placebo
  + Baseline to 3-months: 1.24 (p-value = 0.88)
  + Baseline to 12-months: -3.27 (p-value = 0.69)



figures/predictedNormalizedConcRatio.png

### Normalized GSH concentration

* Normalized GSH concentration was not significantly different between study arm or visits

### Normalized GSSG concentration

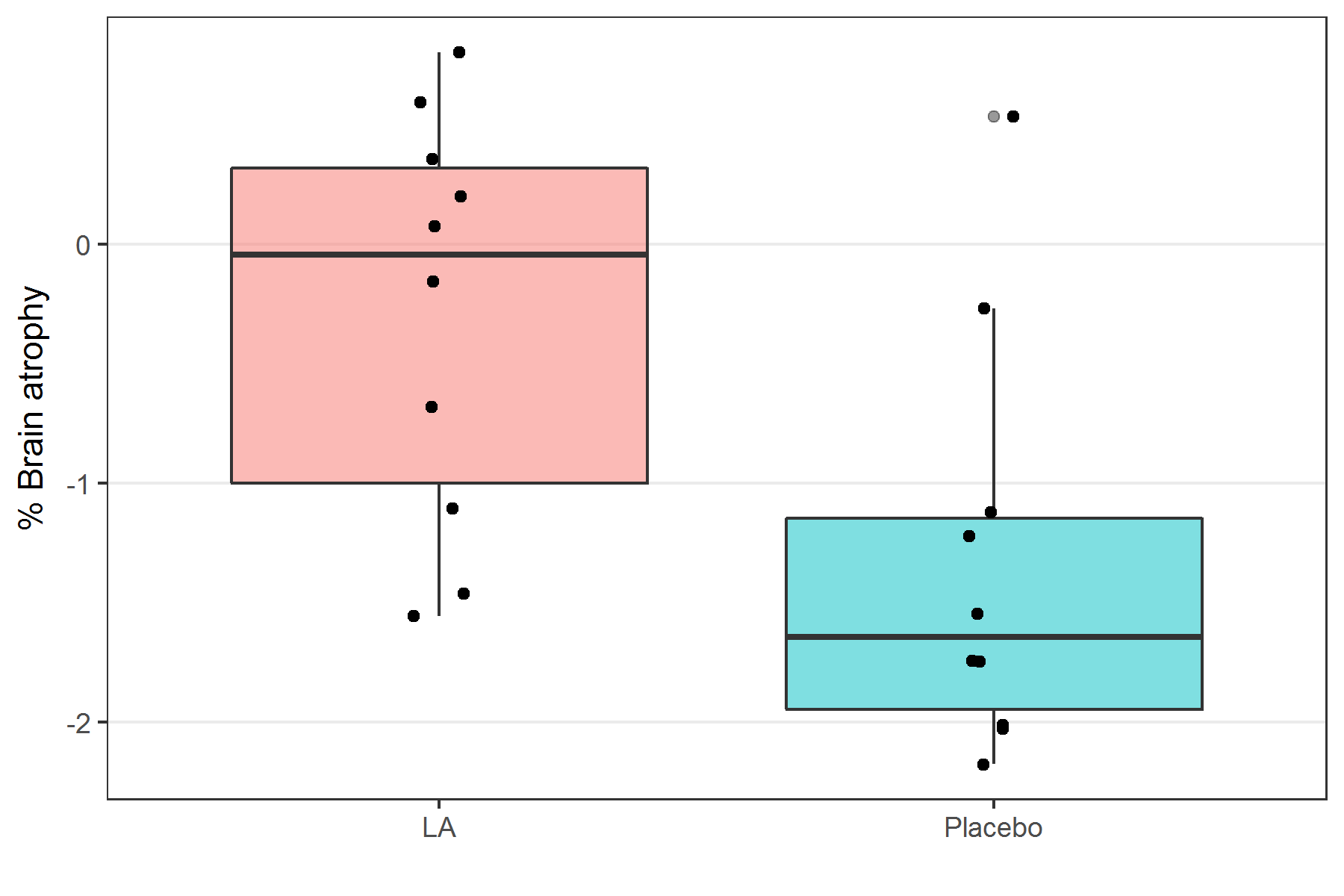
* Normalized GSSG concentration was not significantly different between study arm or visits

# Aim 2

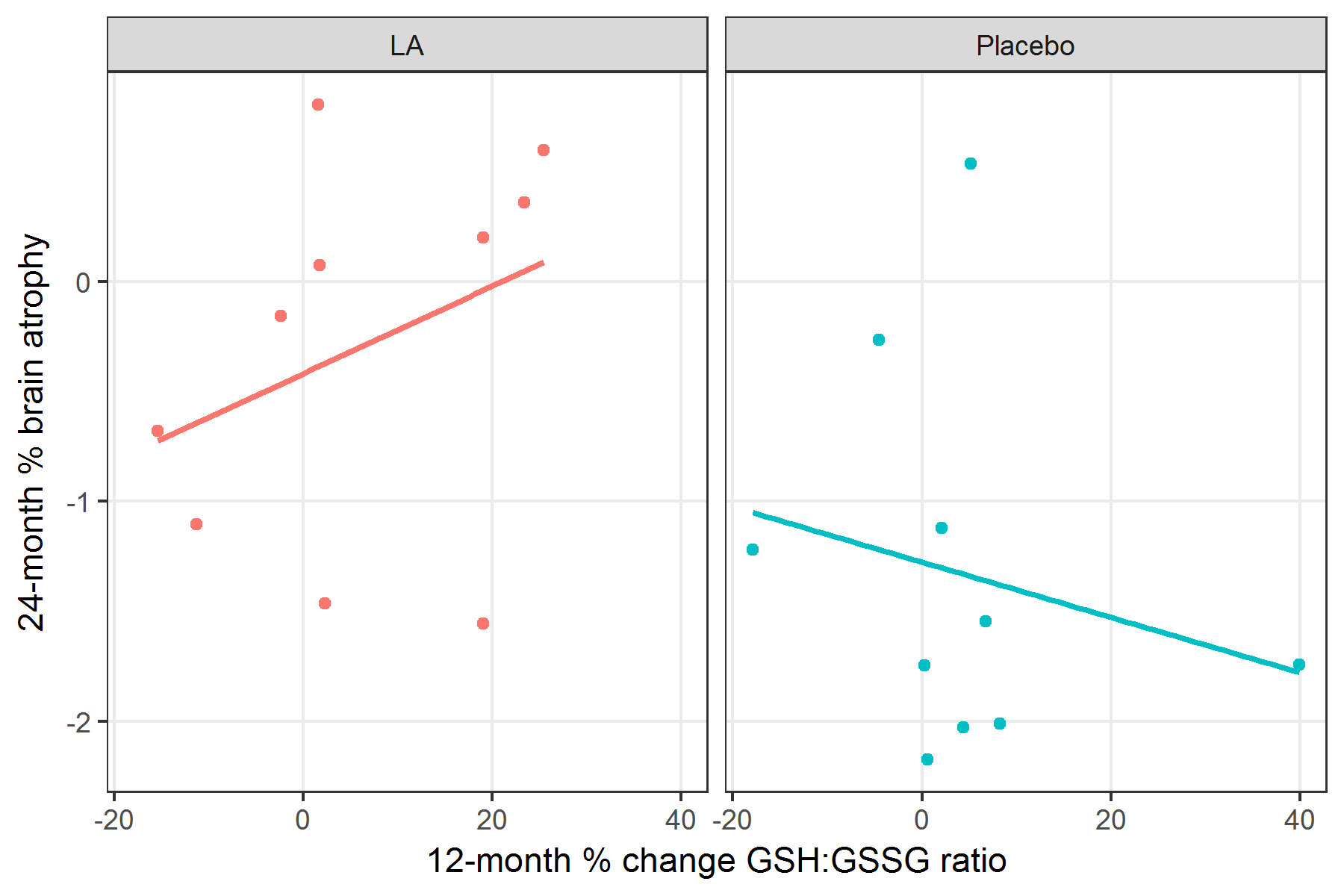
The model for Aim 2 will be a linear regression model.

The model is

## 24-month brain atrophy



figures/boxplotBrainAtrophy.png



figures/scatterplotBrainAtrophy.png

Linear model.

##   
## Call:  
## lm(formula = brainAtrophy ~ pctChangeConcRatio, data = df2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -1.3330 -0.8445 -0.2278 0.9139 1.6401   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) -0.845579 0.243916 -3.467 0.00275 \*\*  
## pctChangeConcRatio 0.006138 0.016436 0.373 0.71316   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 1.015 on 18 degrees of freedom  
## Multiple R-squared: 0.007689, Adjusted R-squared: -0.04744   
## F-statistic: 0.1395 on 1 and 18 DF, p-value: 0.7132

##   
## Call:  
## lm(formula = brainAtrophy ~ pctChangeConcRatio + studyArm, data = df2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -1.30784 -0.69327 -0.02638 0.48161 1.86379   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) -0.315742 0.293528 -1.076 0.2971   
## pctChangeConcRatio 0.003663 0.014321 0.256 0.8012   
## studyArmPlacebo -1.032810 0.395621 -2.611 0.0183 \*  
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 0.8827 on 17 degrees of freedom  
## Multiple R-squared: 0.2917, Adjusted R-squared: 0.2083   
## F-statistic: 3.5 on 2 and 17 DF, p-value: 0.05334

##   
## Call:  
## lm(formula = brainAtrophy ~ pctChangeConcRatio + studyArm + pctChangeConcRatio:studyArm,   
## data = df2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -1.51347 -0.50883 0.03996 0.34823 1.87493   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) -0.41864 0.30452 -1.375 0.1882   
## pctChangeConcRatio 0.01989 0.02008 0.991 0.3365   
## studyArmPlacebo -0.85676 0.42126 -2.034 0.0589 .  
## pctChangeConcRatio:studyArmPlacebo -0.03245 0.02839 -1.143 0.2698   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 0.8748 on 16 degrees of freedom  
## Multiple R-squared: 0.3451, Adjusted R-squared: 0.2224   
## F-statistic: 2.811 on 3 and 16 DF, p-value: 0.07279

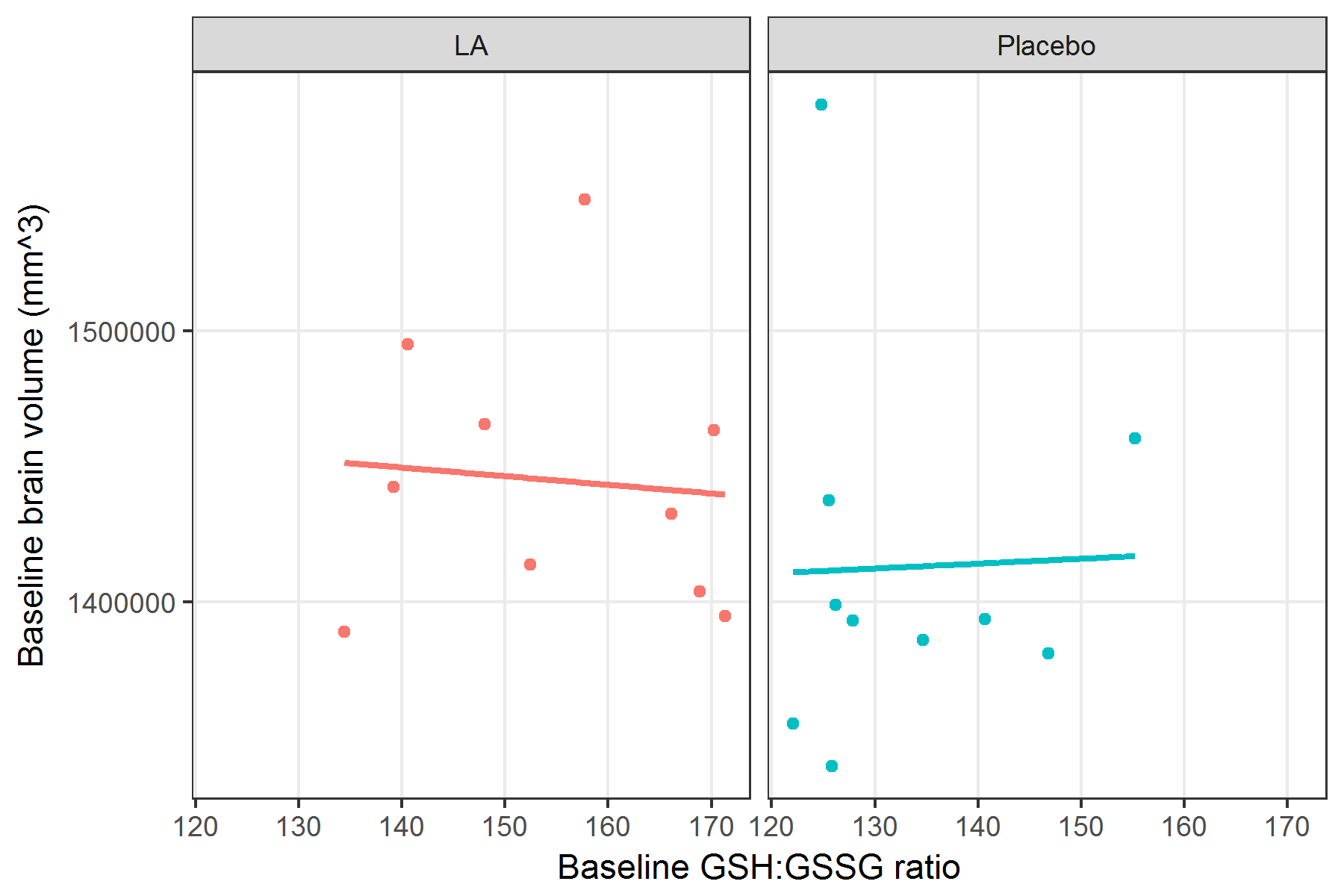
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| term | estimate | std.error | statistic | p.value |
| (Intercept) | -0.42 | 0.30 | -1.37 | 0.1882 |
| pctChangeConcRatio | 0.02 | 0.02 | 0.99 | 0.3365 |
| studyArmPlacebo | -0.86 | 0.42 | -2.03 | 0.0589 |
| pctChangeConcRatio:studyArmPlacebo | -0.03 | 0.03 | -1.14 | 0.2698 |

Details (not shown).

## Interpretation

* Percent brain atrophy was not significantly associated with GSH:GSSG concentration change
  + of 0.00614 (p-value = 0.713)
  + Correlation coefficient = 0.0877
  + GSH:GSSG concentration change explains 0.769% of the variation in brain atrophy
* The association was still not significant after adjusting for study arm
  + of 0.00366 (p-value = 0.801)
  + Partial correlation coefficient = 0.0619
  + GSH:GSSG concentration change explains 0.383% of the variation in brain atrophy after adjusting for study arm

## Crosssectional correlation between baseline GSH:GSSG ratio and brain volume



figures/scatterplotBrainVolumeAtBaseline.png

Linear model.

##   
## Call:  
## lm(formula = wholeBrainVol ~ concRatioM0, data = df2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -78569 -37987 -19742 20919 165697   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) 1343187.3 123322.1 10.892 2.36e-09 \*\*\*  
## concRatioM0 595.0 851.3 0.699 0.494   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 61870 on 18 degrees of freedom  
## Multiple R-squared: 0.02642, Adjusted R-squared: -0.02767   
## F-statistic: 0.4884 on 1 and 18 DF, p-value: 0.4936

##   
## Call:  
## lm(formula = wholeBrainVol ~ concRatioM0 + studyArm, data = df2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -74254 -33370 -16480 21317 169276   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) 1464256.0 180476.2 8.113 3.01e-07 \*\*\*  
## concRatioM0 -125.5 1158.2 -0.108 0.915   
## studyArmPlacebo -34709.5 37638.6 -0.922 0.369   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 62120 on 17 degrees of freedom  
## Multiple R-squared: 0.0728, Adjusted R-squared: -0.03628   
## F-statistic: 0.6674 on 2 and 17 DF, p-value: 0.526

### Interpretation

* Baseline whole brain volume was not significantly associated with baseline GSH:GSSG concentration ratio
  + of 595 (p-value = 0.494)
  + Correlation coefficient = 0.163
  + Baseline GSH:GSSG concentration ratio explains 2.64% of the variation in brain atrophy
* The association was still not significant after adjusting for study arm
  + of -126 (p-value = 0.915)
  + Partial correlation coefficient = -0.0263
  + Baseline GSH:GSSG concentration ratio explains 0.0691% of the variation in brain atrophy after adjusting for study arm