Example from data programming to report

Modeling Memo

**dd-Mmm-yyyy**

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# Background

This memo was generated as an example. No care was taken to make it look nice or to ensure the adequacy of the selected model. The main purpose was to show how generated information in R can easily be included in Word. Formatting of tables, style of figures, and Word style can be fully customized.

* Example analysis from SAS source data to modeling results
* **Based on fake source data**

# Data

PopPK modeling dataset was prepared according to specs defined in [Section](#dataspec)UPDATE REFERENCE. Following modifications to the data were done:

* Manually excluded observation records: Appendix UPDATE REFERENCE
* Excluded observation records with missing time: Appendix UPDATE REFERENCE
* Excluded observation records with missing observation: Appendix UPDATE REFERENCE
* Manually excluded subjects: Appendix UPDATE REFERENCE
* Excluded placebo subjects: Appendix UPDATE REFERENCE
* Excluded subjects without observations: Appendix UPDATE REFERENCE
* Removed dose records with zero amount: Appendix UPDATE REFERENCE
* Covariate imputations: Appendix UPDATE REFERENCE

###### Table Demographics table - continuous

|  |  |  |
| --- | --- | --- |
| Characteristic | HS0815-01 [N=24] | TOTAL [N=24] |
| Age (years) | 30.8 (10) [18-51] | 30.8 (10) [18-51] |
| Height (cm) | 171 (6.34) [157-182] | 171 (6.34) [157-182] |
| Weight (kg) | 66.3 (9.59) [46.8-84.4] | 66.3 (9.59) [46.8-84.4] |
| Albumin (g/dL) | 4.42 (0.269) [3.8-5] | 4.42 (0.269) [3.8-5] |
| Creatine Kinase (U/L) | 190 (102) [48-444] | 190 (102) [48-444] |

N: Number of subjects  
Entries represent: Mean (Standard deviation) [Minimum-Maximum]

../Output/03\_exploreNLMEdata/TAB01\_summaryCovPK.txt

SCRIPT\_03\_exploreNLMEdata.R

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###### Table Demographics table - categorical

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Category | HS0815-01 [N=24] | TOTAL [N=24] |
| Gender | M | 16 (66.7%) | 16 (66.7%) |
|  | F | 8 (33.3%) | 8 (33.3%) |
| Race | WHITE | 4 (16.7%) | 4 (16.7%) |
|  | OTHER | 20 (83.3%) | 20 (83.3%) |

N: Number of subjects  
Number of subjects in each category and percentage within this category

../Output/03\_exploreNLMEdata/TAB02\_summaryCatPK.txt

SCRIPT\_03\_exploreNLMEdata.R

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###### Table Summary of available observations

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Data | N subjects\* | N samples | N BLOQ samples\*\* | N BLOQ samples post first dose\* | N missing observations | N missing time information | N total ignored observations | N samples included in analysis |
| HS0815-01 | 24 / 24 | 329 | 24 (7.29%) | 0 (0%) | 0 (0%) | 0 (0%) | 24 (7.29%) | 305 (92.7%) |
| TOTAL | 24 / 24 | 329 | 24 (7.29%) | 0 (0%) | 0 (0%) | 0 (0%) | 24 (7.29%) | 305 (92.7%) |

N: Number of  
\* All subjects / subjects with at least one non missing (MDV==0) sample.  
\*\* These records are excluded from the analysis (M1 method).

../Output/03\_exploreNLMEdata/TAB03\_summaryObsPK.txt

SCRIPT\_03\_exploreNLMEdata.R

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Correlation of potential covariates are shown in Appendix UPDATE REFERENCE, UPDATE REFERENCE, and UPDATE REFERENCE.

# Model Results

* All tested models shown in Appendix UPDATE REFERENCE
* Key model results shown in UPDATE REFERENCE
* Final selected model results shown in UPDATE REFERENCE
  + Prediction corrected VPC shown in UPDATE REFERENCE
  + Diagnostics shown in [Section](#diagnostics)UPDATE REFERENCE
  + Final model control file in Appendix UPDATE REFERENCE
  + Final model output file in Appendix UPDATE REFERENCE

###### Table Key model results

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | 01\_BASEMODEL | 02\_COVARIATEMODEL | 03\_FINALMODEL |
| CL | 0.148 (13%) | 0.148 (17%) | 0.147 (11%) |
| Vc | 2.77 (7.5%) | 2.73 (8.8%) | 2.71 (5.6%) |
| Q1 | 0.48 (12%) | 0.484 (12%) | 0.481 (12%) |
| Vp1 | 2.3 (9.2%) | 2.3 (10%) | 2.3 (11%) |
|  |  |  |  |
| omega(CL) | 0.272 (21%) | 0.272 (23%) | 0.276 (22%) |
| omega(Vc) | 0.178 (21%) | 0.153 (24%) | 0.154 (22%) |
| omega(Q1) | 0.1 (FIX) | 0.1 (FIX) | 0.1 (FIX) |
| omega(Vp1) | 0.251 (26%) | 0.257 (28%) | 0.261 (28%) |
|  |  |  |  |
| beta\_Vc(AGE0) | - | 0.233 (47%) | 0.324 (24%) |
|  |  |  |  |
| corr(CL,Vc) | - | - | 0.822 (19%) |
|  |  |  |  |
| error\_ADD1 | 0.314 (41%) | 0.313 (44%) | 0.322 (47%) |
| error\_PROP1 | 0.109 (5.7%) | 0.108 (5.8%) | 0.107 (5.9%) |
|  |  |  |  |
| OBJ | 1502 | 1496 | 1474 |
| BIC | 1553 | 1553 | 1537 |
| AIC | 1520 | 1516 | 1496 |

FIX (parameter fixed to this value), - (parameter not used)  
Number of significant digits: 3.  
Relative standard errors (RSE) given in parenthesis with 2 significant digits.  
Model metrics (OBJ, AIC, BIC) are rounded to nearest integer., 01\_BASEMODEL (../Output/FINALMODELS//01\_BASEMODEL), 02\_COVARIATEMODEL (../Output/FINALMODELS//02\_COVARIATEMODEL), 03\_FINALMODEL (../Output/FINALMODELS//03\_FINALMODEL)

../Output/FINALMODELS/TAB\_01\_comparison.txt

SCRIPT\_30\_FinalModel.R

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###### Table Final selected model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| PARAMETER | VALUE | RSE | SHRINKAGE | COMMENT |
| **Typical parameters** |  |  |  |  |
| CL | 0.147 | 11.2% | - | Clearance (L/hour) |
| Vc | 2.71 | 5.59% | - | Central volume (L) |
| Q1 | 0.481 | 12.5% | - | Intercompartmental clearance (L/hour) |
| Vp1 | 2.3 | 11% | - | Peripheral volume (L) |
|  |  |  |  |  |
| **Inter-individual variability** |  |  |  |  |
| omega(CL) | 0.276 | 21.6% | -0.5% | LogNormal |
| omega(Vc) | 0.154 | 21.8% | 3.7% | LogNormal |
| omega(Q1) | 0.1 (FIX) | - | 71.1% | LogNormal |
| omega(Vp1) | 0.261 | 28.2% | 9.6% | LogNormal |
|  |  |  |  |  |
| **Correlation of random effects** |  |  |  |  |
| corr(CL,Vc) | 0.822 | 19.3% | - | Correlation coefficient |
|  |  |  |  |  |
| **Parameter-Covariate relationships** |  |  |  |  |
| beta\_Vc(AGE0) | 0.324 | 23.7% | - | Age in years on Vc (centered around: 27.5 years) |
|  |  |  |  |  |
| **Residual Variability** |  |  |  |  |
| error\_ADD1 | 0.322 | 47.4% | 9.63%\* | Additive Error (ug/mL) - Plasma Concentration |
| error\_PROP1 | 0.107 | 5.94% | - | Proportional Error (fraction) - Plasma Concentration |
|  |  |  |  |  |
| Objective function | 1474 | - | - | - |
| AIC | 1496 | - | - | - |
| BIC | 1537 | - | - | - |

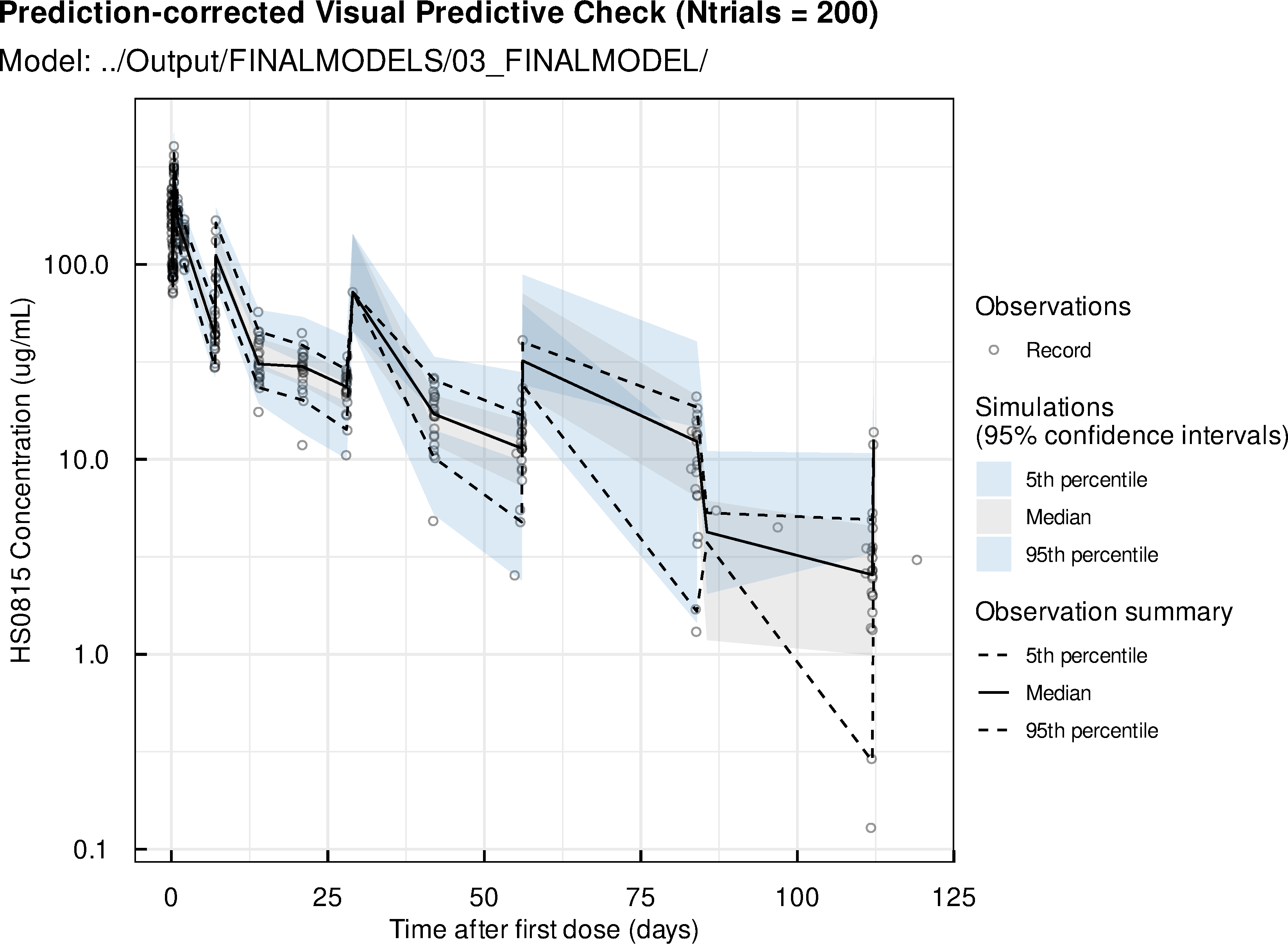
Model: ../Models/04\_covariance\_modeling/MODELCOR01, Significant digits: 3 (Objective function rounded to closest integer value), omega values and error model parameters reported in standard deviation.  
As suggested in the NONMEM manual, the objective function was determined using importance sampling (IMP) with settings EONLY=1 and MAPITER=0.  
\* Epsilon shrinkage (records with missing dependent variable and censored records not considered).

../Models/04\_covariance\_modeling/MODELCOR01/project\_parameters\_table.txt

SCRIPT\_25\_PK\_covariance.R

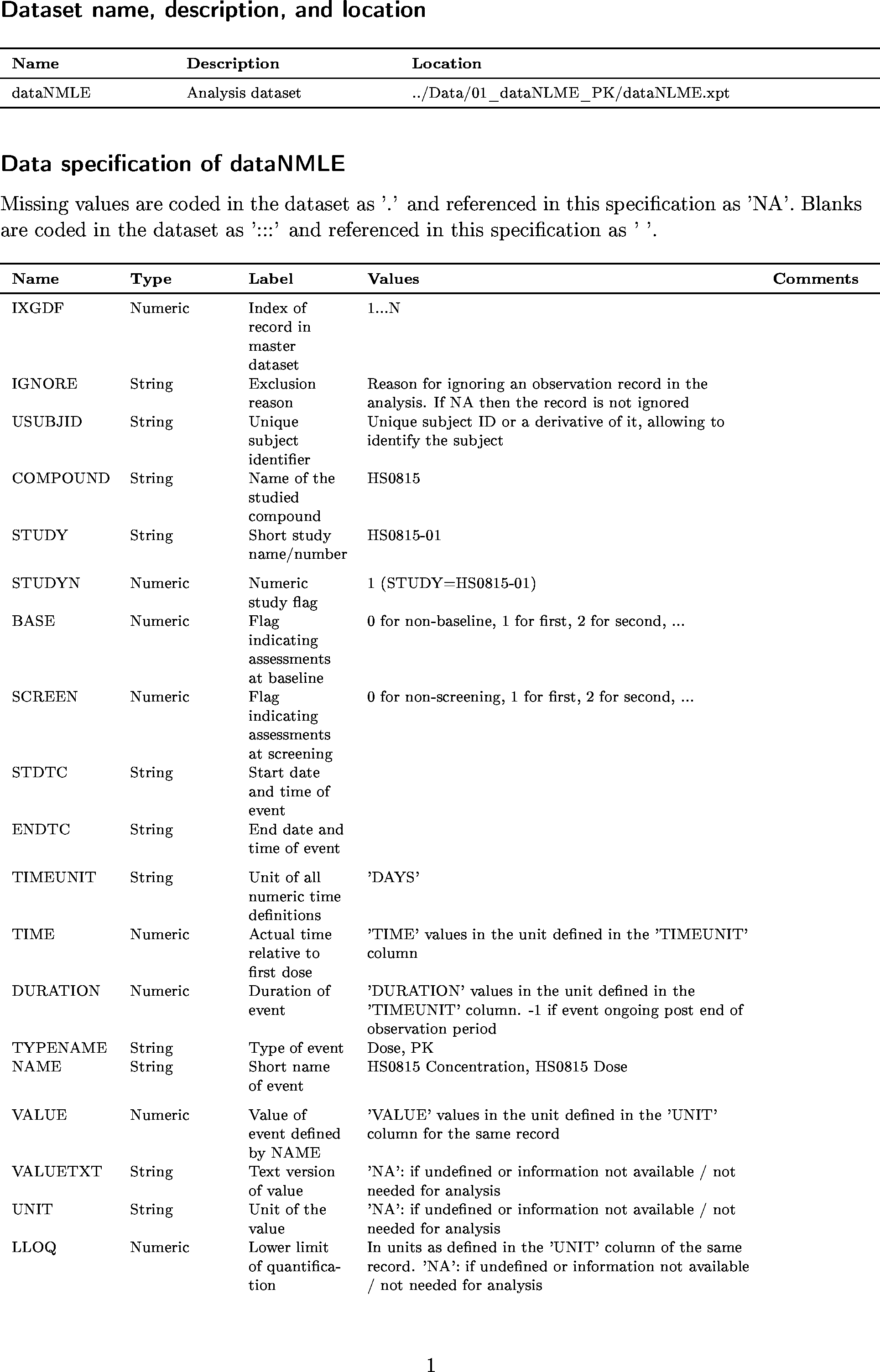
2023-09-11 15:19:29

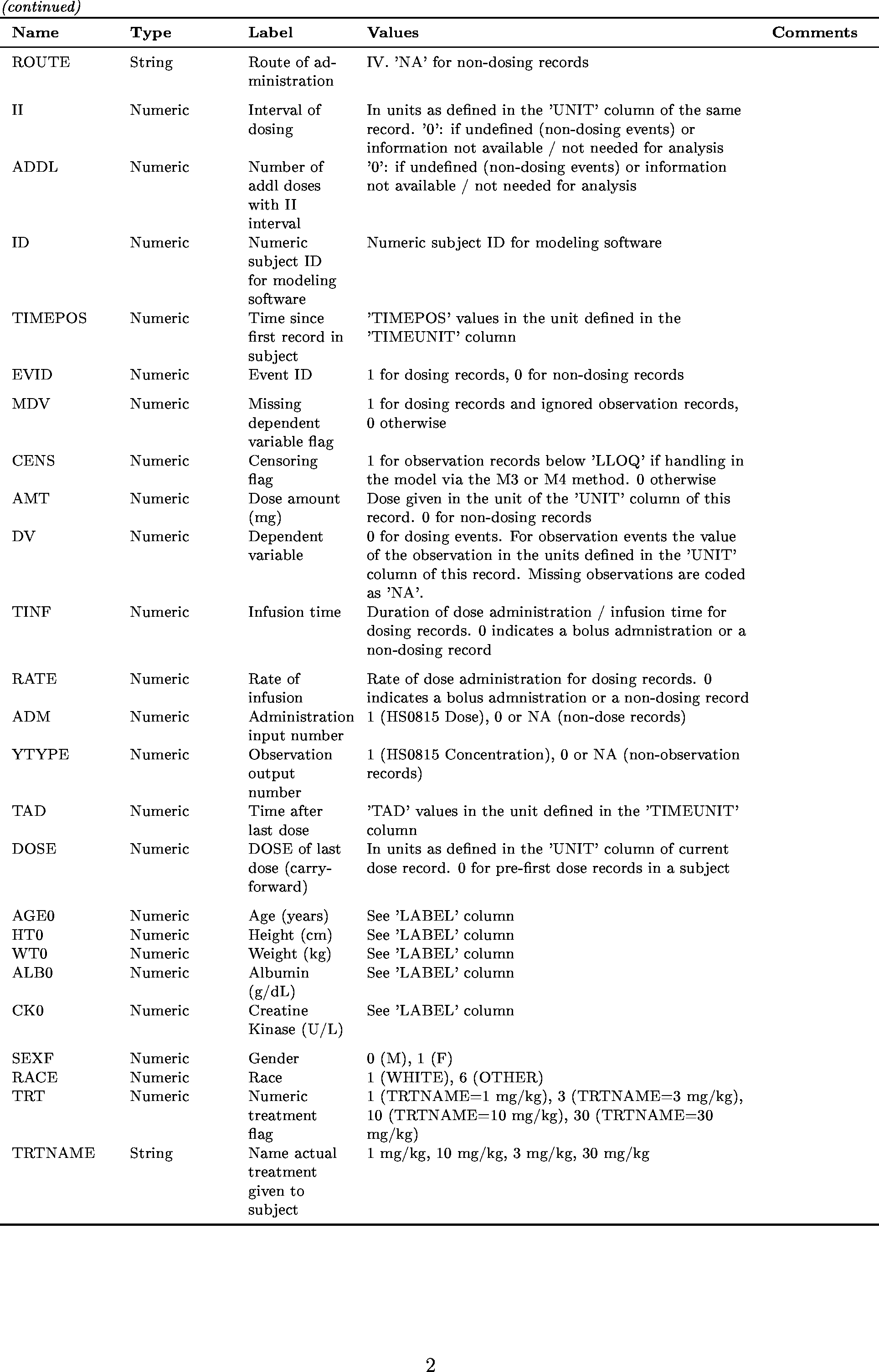
Figure Prediction corrected VPC for final selected model



../Output/FINALMODELS/FIG01\_pcVPC\_FINALMODEL\_1.pdf  
SCRIPT\_30\_FinalModel.R  
2023-09-11 15:20:29

# Data Specification





# Data Programming

###### Table Manually selected ignored observation records

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IXGDF | USUBJID | NAME | TIME | TAD | EVID | DV | MDV | IGNORE |
| 5 | HS0815-01-001-001 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 28 | HS0815-01-001-002 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 50 | HS0815-01-001-003 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 73 | HS0815-01-001-011 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 96 | HS0815-01-001-014 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 119 | HS0815-01-001-017 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 142 | HS0815-01-001-023 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 165 | HS0815-01-001-049 | HS0815 Concentration | -0.00902777777810115 | -0.00902777777810115 | 0 | 0 | 1 | Pre-first-dose samples |
| 187 | HS0815-01-001-050 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 210 | HS0815-01-001-051 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 233 | HS0815-01-001-053 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 256 | HS0815-01-001-057 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 279 | HS0815-01-001-058 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 302 | HS0815-01-001-061 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 325 | HS0815-01-001-063 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 348 | HS0815-01-001-067 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 371 | HS0815-01-001-074 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 394 | HS0815-01-001-075 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 417 | HS0815-01-001-076 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 440 | HS0815-01-001-078 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 463 | HS0815-01-001-088 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 486 | HS0815-01-001-104 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 509 | HS0815-01-001-107 | HS0815 Concentration | -0.00347222222626442 | -0.00347222222626442 | 0 | 0 | 1 | Pre-first-dose samples |
| 532 | HS0815-01-001-108 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 548 | HS0815-01-001-120 | HS0815 Concentration | -0.0104166666678793 | -0.0104166666678793 | 0 | 0 | 1 | Pre-first-dose samples |
| 571 | HS0815-01-001-124 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 594 | HS0815-01-001-130 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 617 | HS0815-01-001-132 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 640 | HS0815-01-001-136 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |
| 663 | HS0815-01-001-142 | HS0815 Concentration | -0.00624999999854481 | -0.00624999999854481 | 0 | 0 | 1 | Pre-first-dose samples |
| 686 | HS0815-01-001-143 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 709 | HS0815-01-001-145 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 732 | HS0815-01-001-156 | HS0815 Concentration | -0.00624999999854481 | -0.00624999999854481 | 0 | 0 | 1 | Pre-first-dose samples |
| 755 | HS0815-01-001-175 | HS0815 Concentration | -0.00694444444161491 | -0.00694444444161491 | 0 | 0 | 1 | Pre-first-dose samples |
| 778 | HS0815-01-001-502 | HS0815 Concentration | -0.00555555555911269 | -0.00555555555911269 | 0 | 0 | 1 | Pre-first-dose samples |
| 815 | HS0815-01-001-520 | HS0815 Concentration | -0.00694444444525288 | -0.00694444444525288 | 0 | 0 | 1 | Pre-first-dose samples |

Rule for IGNORE: user defined input

../Output/02\_createNLMEdata/01\_datacleaning/01\_Manually\_Selected\_Records.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table Observation records with missing time

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| IXGDF | USUBJID | NAME | TIME | DV |
| - | - | - | - | - |

Rule for removal: EVID==0 & is.na(TIME)

../Output/02\_createNLMEdata/01\_datacleaning/02\_Missing\_TIME\_Observation\_Records.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table Observation records with missing value

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IXGDF | USUBJID | NAME | TIME | DV | MDV | IGNORE |
| 770 | HS0815-01-001-175 | HS0815 Concentration | 41.9937500000015 | NA | 1 | Missing value |

Rule for ignoring: EVID==0 & is.na(DV)

../Output/02\_createNLMEdata/01\_datacleaning/03\_Missing\_DV\_Observation\_Records.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table N=0 subjects removed from the data

|  |  |
| --- | --- |
| USUBJID | REMOVE.REASON |
| - | No subjects removed |

Rule for removal: user defined input

../Output/02\_createNLMEdata/01\_datacleaning/04\_Manually\_Selected\_Subjects.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table N=12 placebo subjects have been removed

|  |  |
| --- | --- |
| USUBJID | REMOVAL.REASON |
| HS0815-01-001-001 | Placebo Subject |
| HS0815-01-001-002 | Placebo Subject |
| HS0815-01-001-049 | Placebo Subject |
| HS0815-01-001-058 | Placebo Subject |
| HS0815-01-001-075 | Placebo Subject |
| HS0815-01-001-078 | Placebo Subject |
| HS0815-01-001-104 | Placebo Subject |
| HS0815-01-001-142 | Placebo Subject |
| HS0815-01-001-156 | Placebo Subject |
| HS0815-01-001-175 | Placebo Subject |
| HS0815-01-001-502 | Placebo Subject |
| HS0815-01-001-520 | Placebo Subject |

Rule for removal: subject has no dose events or all dose events have AMT=0

../Output/02\_createNLMEdata/01\_datacleaning/06\_Placebo\_Subjects.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table N=0 subjects without MDV=0 observations have been removed

|  |  |
| --- | --- |
| USUBJID | REMOVAL.REASON |
| - | - |

Rule for removal: No observations in subject. Observations defined by EVID=0 & MDV=0 & YTYYPE>0

../Output/02\_createNLMEdata/01\_datacleaning/07\_No\_Observations\_Subjects.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table N=0 dose records with AMT=0 have been removed

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| IXGDF | USUBJID | NAME | TIME | EVID | AMT |
| - | - | - | - | - | - |

Rule for removal: EVID==1 & AMT=0

../Output/02\_createNLMEdata/01\_datacleaning/08\_Zero\_Amount\_Dose\_Records.txt

SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

###### Table Protocol of covariate imputations (N\_Total\_Subjects=24)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| COVNAME | IMPUTATION | VALUES | N.IMPUTED | PERCENT.IMPUTED | USUBJID |
| - | - | - | 0 | 0 | - |

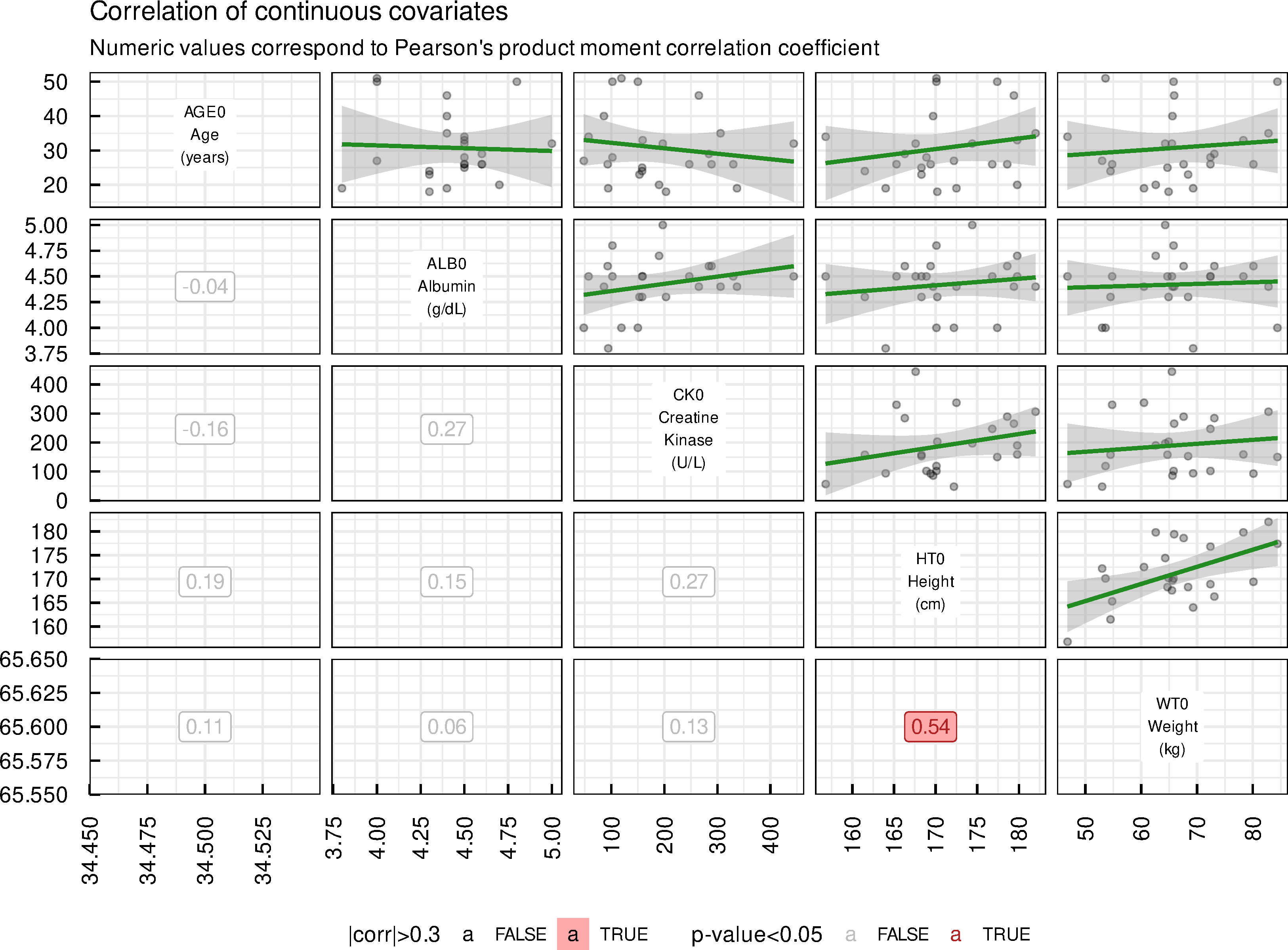
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SCRIPT\_02\_createNLMEdata.R

2023-09-11 15:13:26

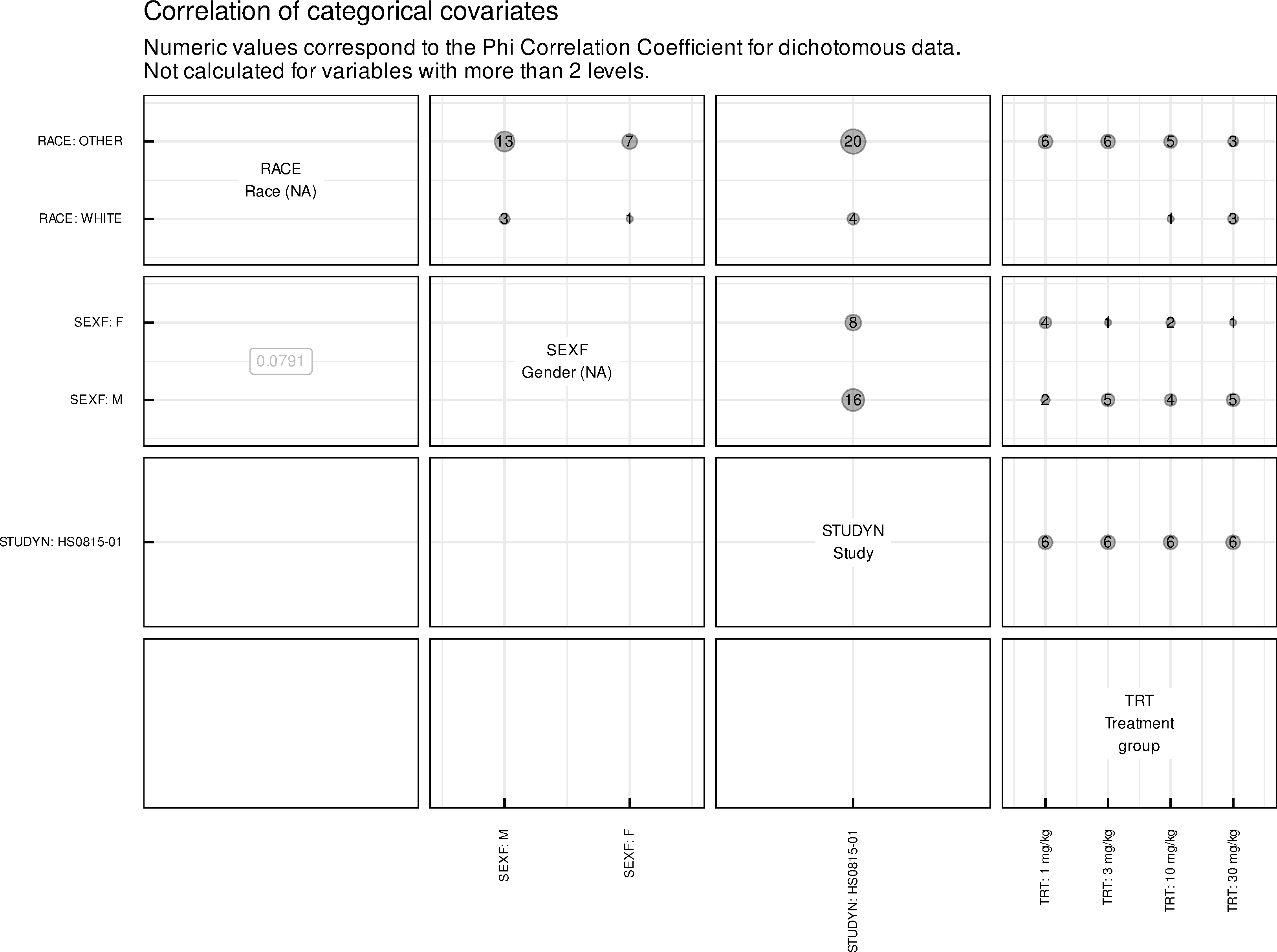
# Data Exploration

Figure Continuous covariate correlation



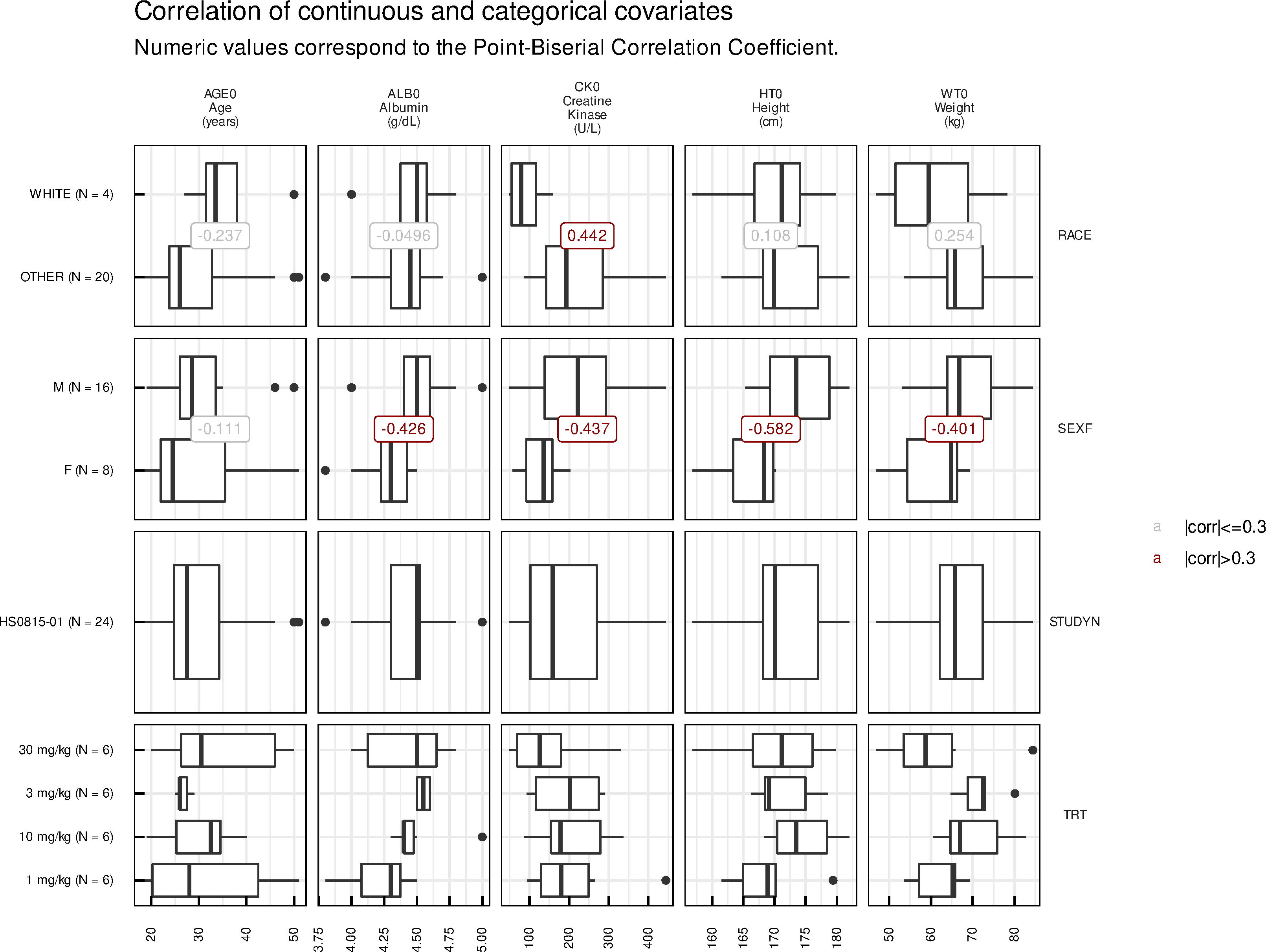
../Output/03\_exploreNLMEdata/01\_dataExploration/05\_ContCovCorrelation.pdf  
SCRIPT\_03\_exploreNLMEdata.R  
2023-09-11 15:13:42

Figure Categorical covariate correlation



../Output/03\_exploreNLMEdata/01\_dataExploration/06\_CatCovCorrelation.pdf  
SCRIPT\_03\_exploreNLMEdata.R  
2023-09-11 15:13:43

Figure Continuous/Categorical covariate correlation



../Output/03\_exploreNLMEdata/01\_dataExploration/07\_ContCatCovCorrelation.pdf  
SCRIPT\_03\_exploreNLMEdata.R  
2023-09-11 15:13:44

# Model development

###### Table Comparison of evaluated models

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| MODEL | OBJ | AIC | BIC | COMMENT |
| 02\_base\_modeling/MODELBASE01 | 1941 | 1953 | 1975 | 1 cpt model |
| 02\_base\_modeling/MODELBASE02 | 1502 | 1522 | 1559 | 2 cpt model |
| 02\_base\_modeling/MODELBASE03 | 1502 | 1520 | 1553 | 2 cpt model - fixed IIV on Q1 (10%CV) |
| 03\_covariate\_modeling/MODELCOV01 | 1496 | 1516 | 1553 | AGE0 on Vc |
| 03\_covariate\_modeling/MODELCOV02 | 1482 | 1506 | 1550 | AGE0 on Vc, SEX on CL and Vc |
| 03\_covariate\_modeling/MODELCOV03 | 1460 | 1494 | 1557 | AGE0 on CL and Vc, SEX on CL and Vc, ALB0 on CL and Vc |
| 04\_covariance\_modeling/MODELCOR01 | 1474 | 1496 | 1537 | CL/Vc |
| 04\_covariance\_modeling/MODELCOR02 | 1461 | 1487 | 1535 | CL/Vc/Vp1 |

Objective functions for MONOLIX and NONMEM models should not be compared with each other!

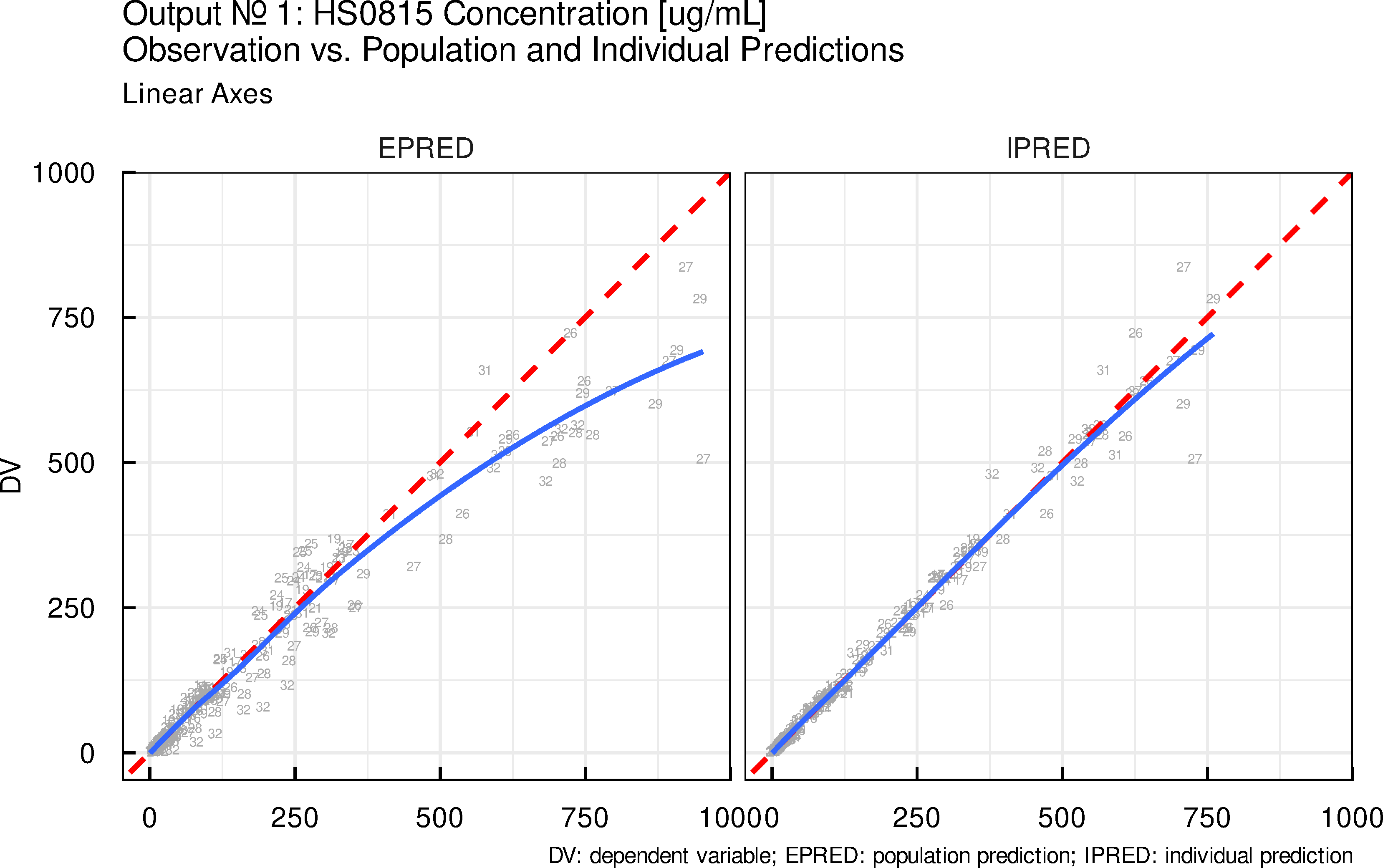
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SCRIPT\_40\_Comparison\_Tables.R

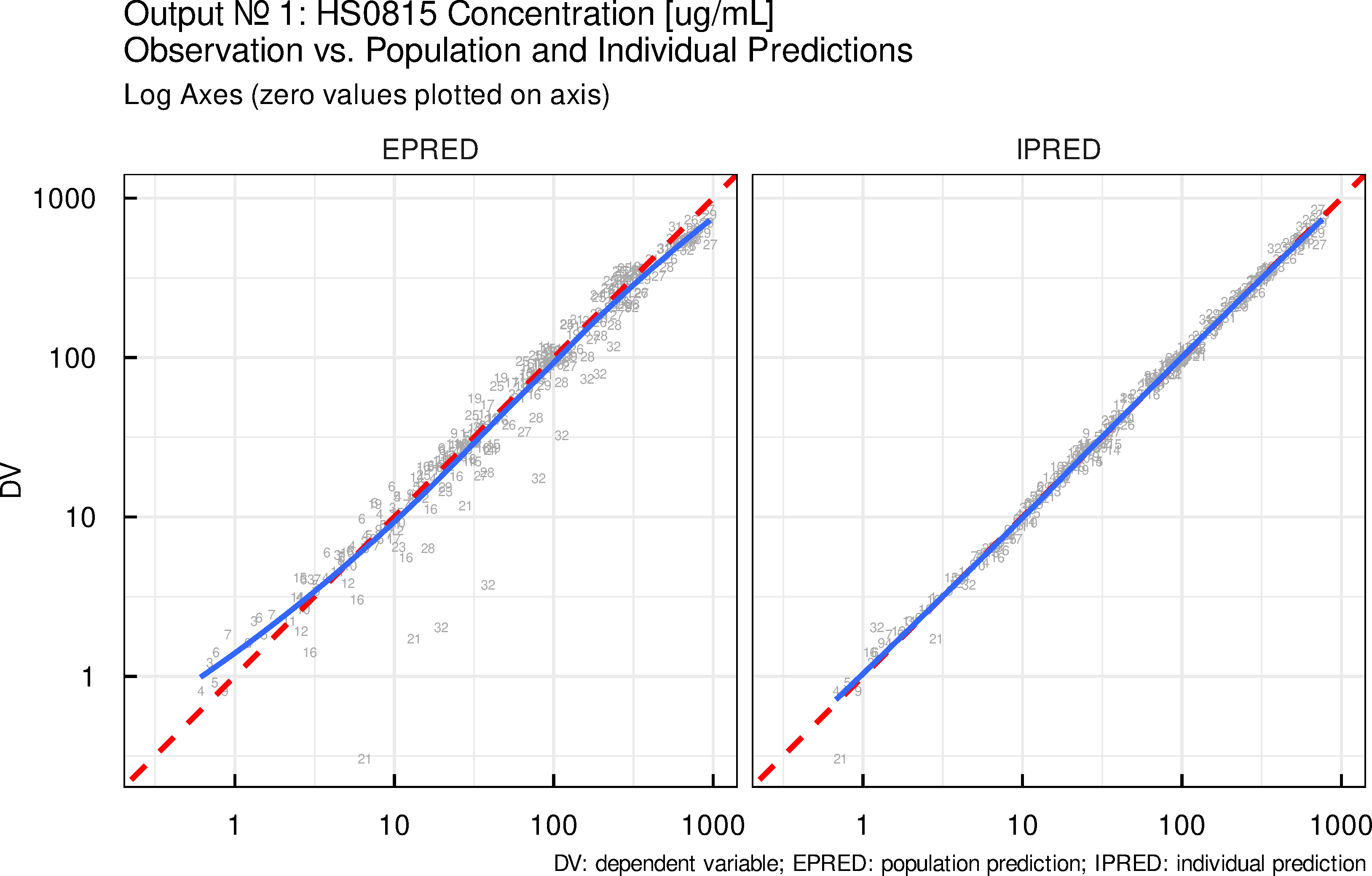
2023-09-11 15:20:29

# Final Model Diagnostics

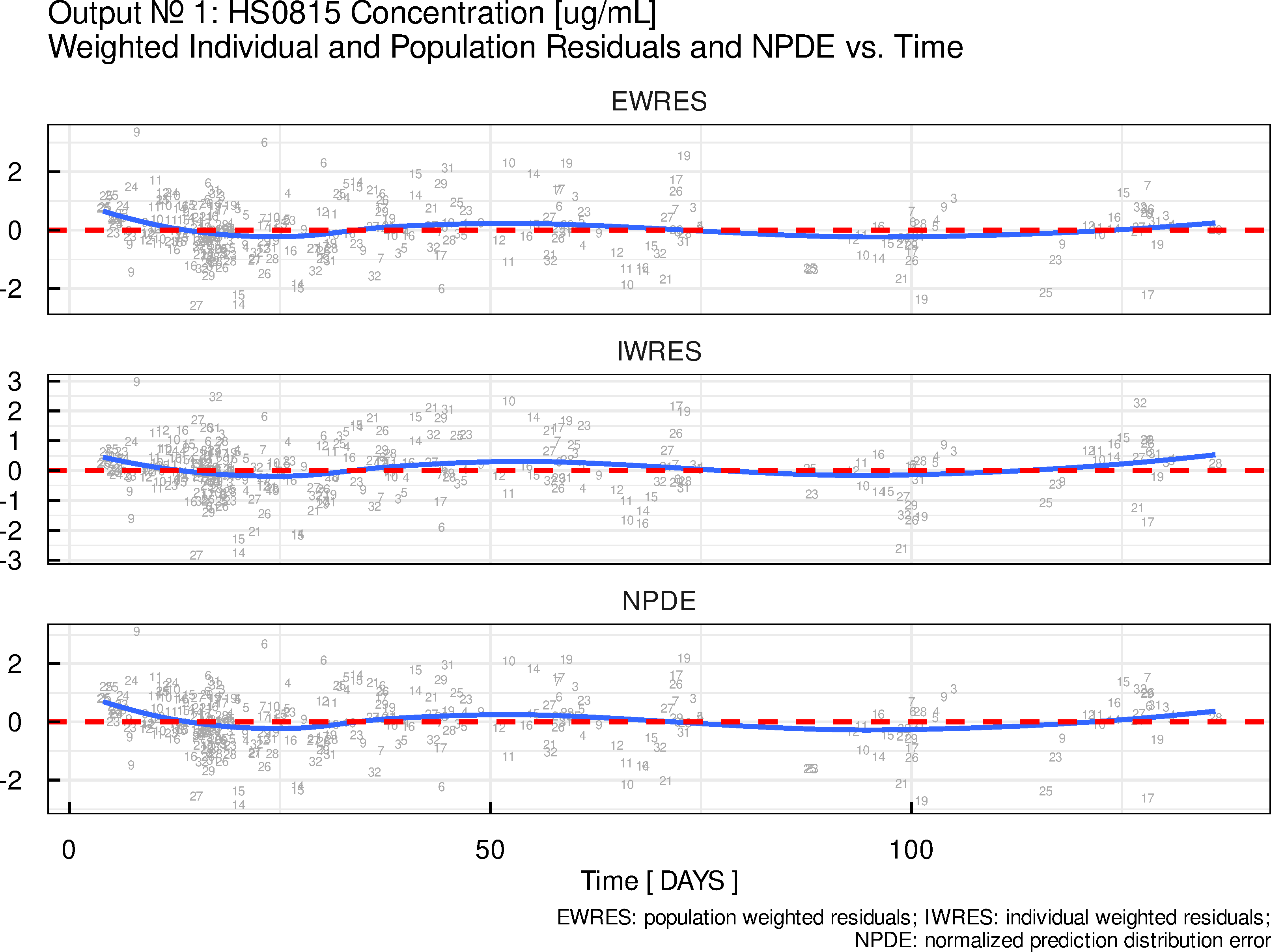
Figure Goodness-of-fit plots



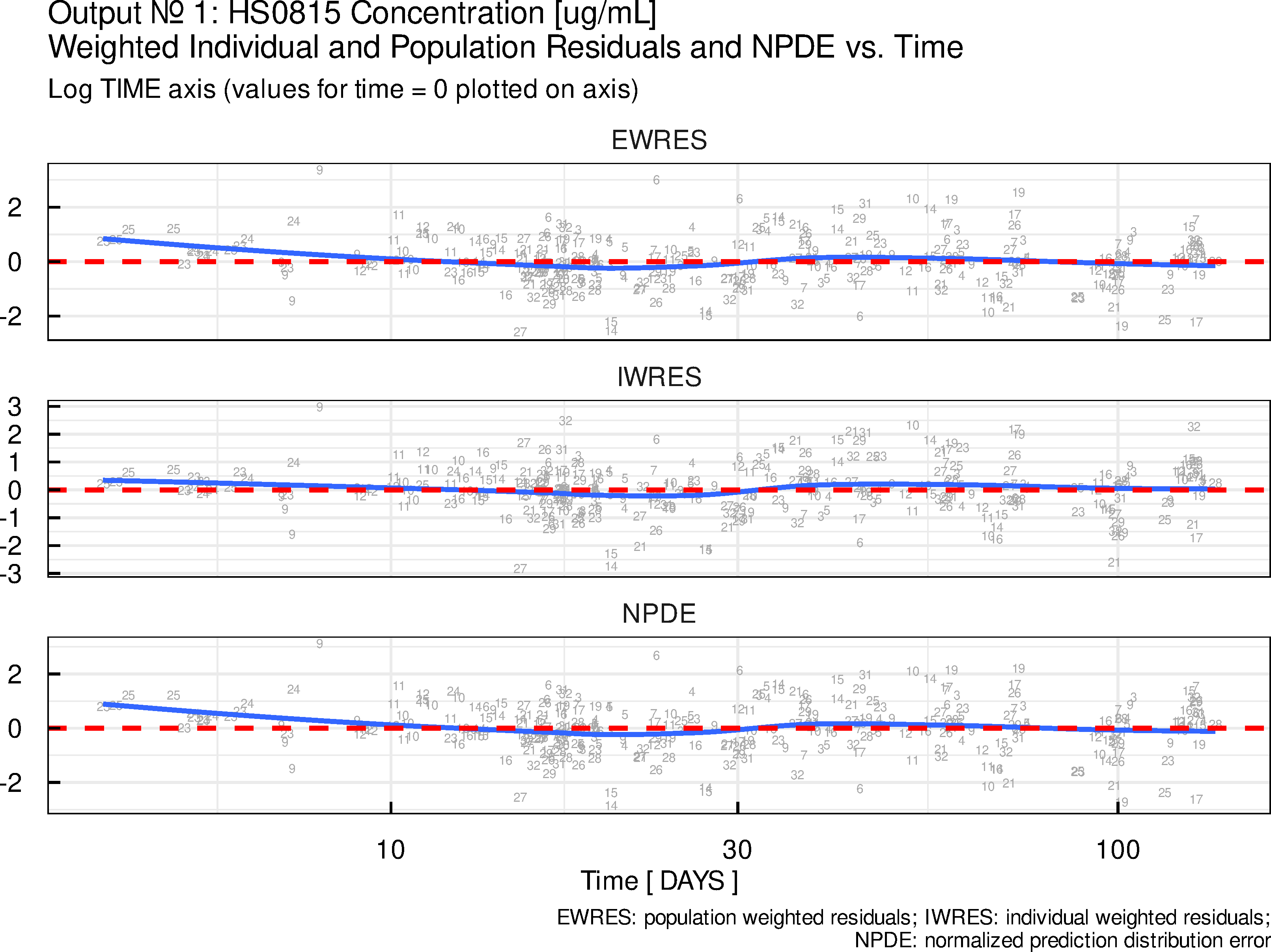
../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_OUTPUT\_1\_Cc/03\_GOF\_Plots.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
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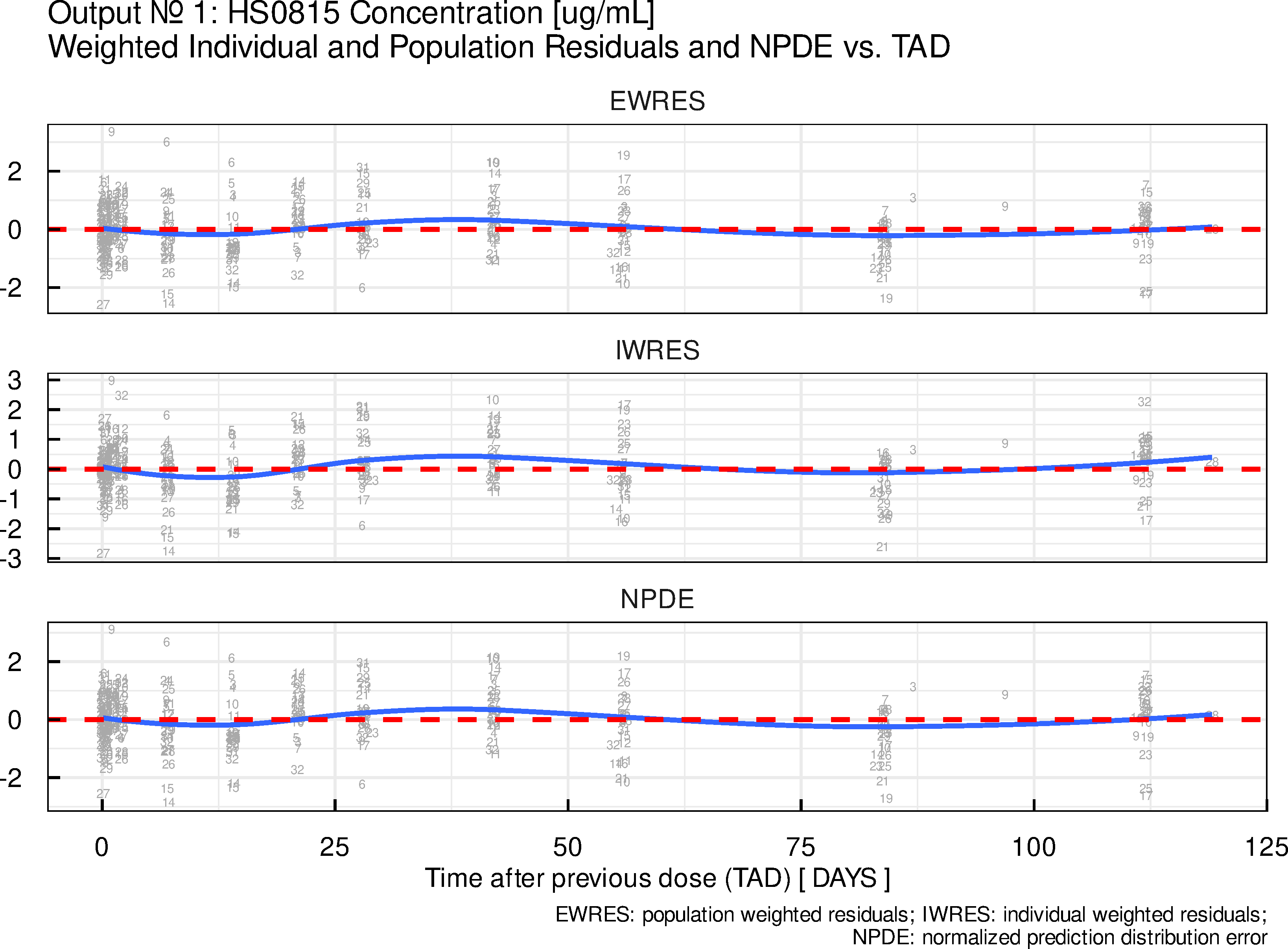
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2023-09-11 15:19:36  
Page 2



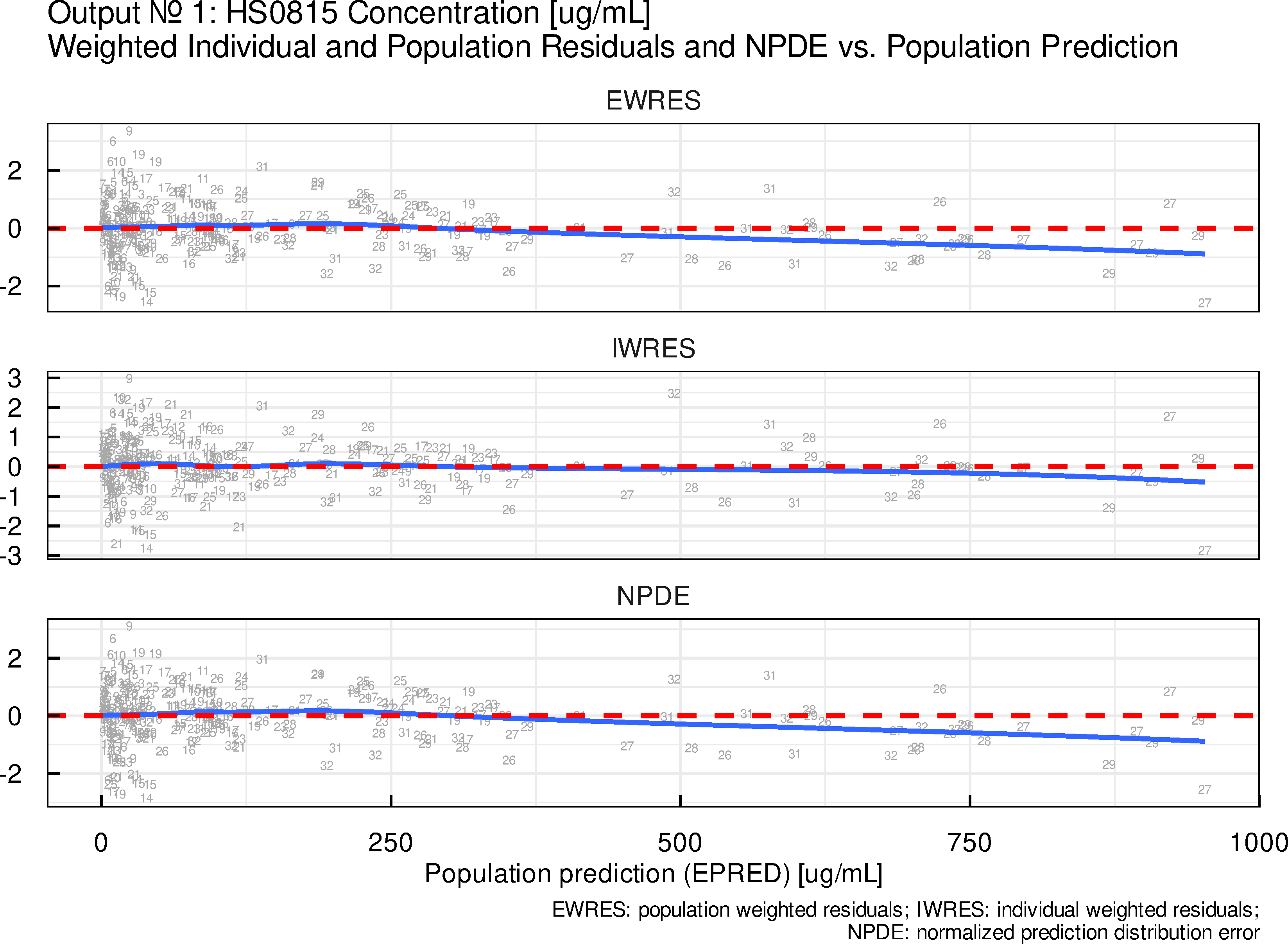
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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
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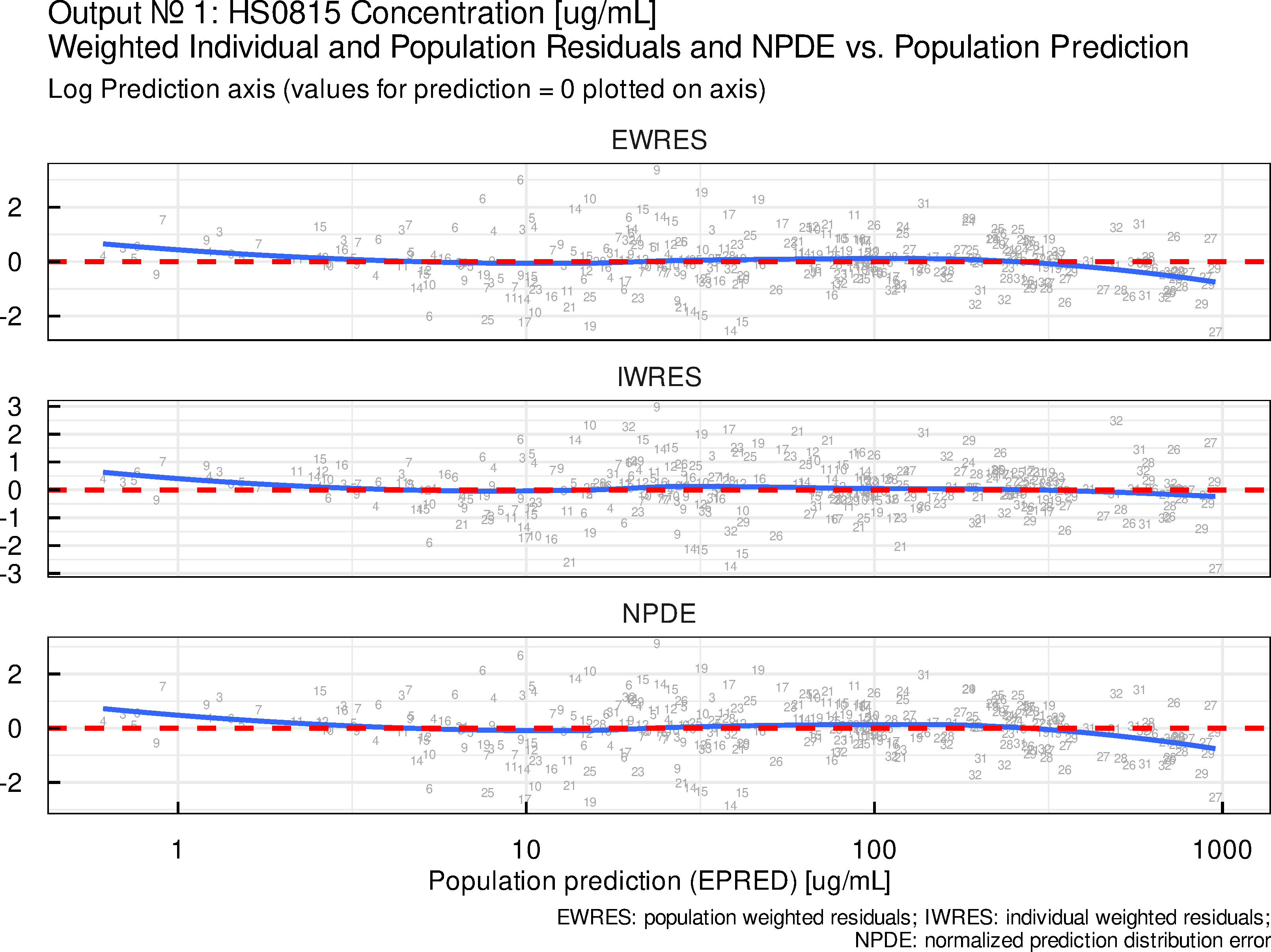
../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_OUTPUT\_1\_Cc/03\_GOF\_Plots.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
Page 4



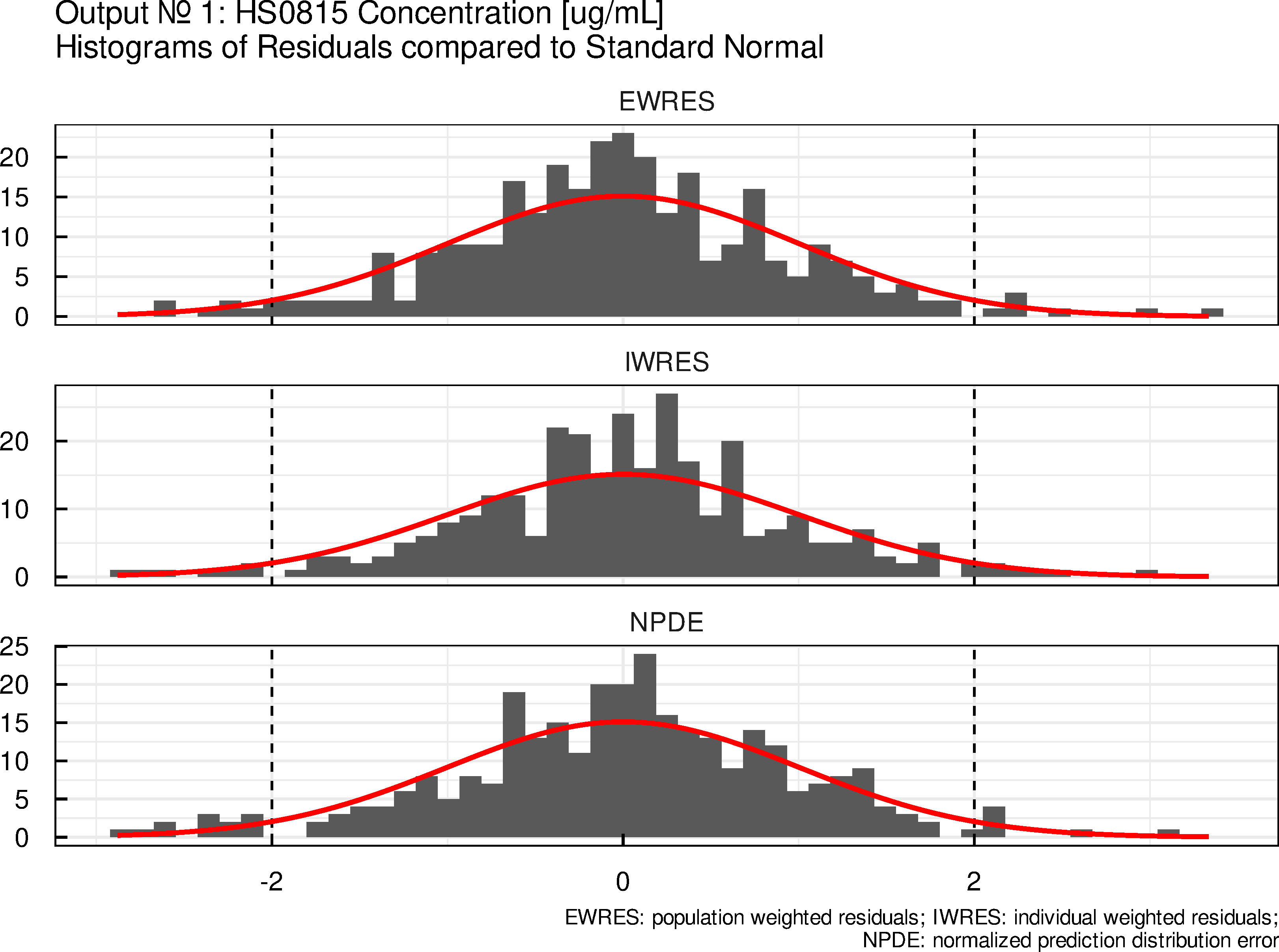
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2023-09-11 15:19:36  
Page 5



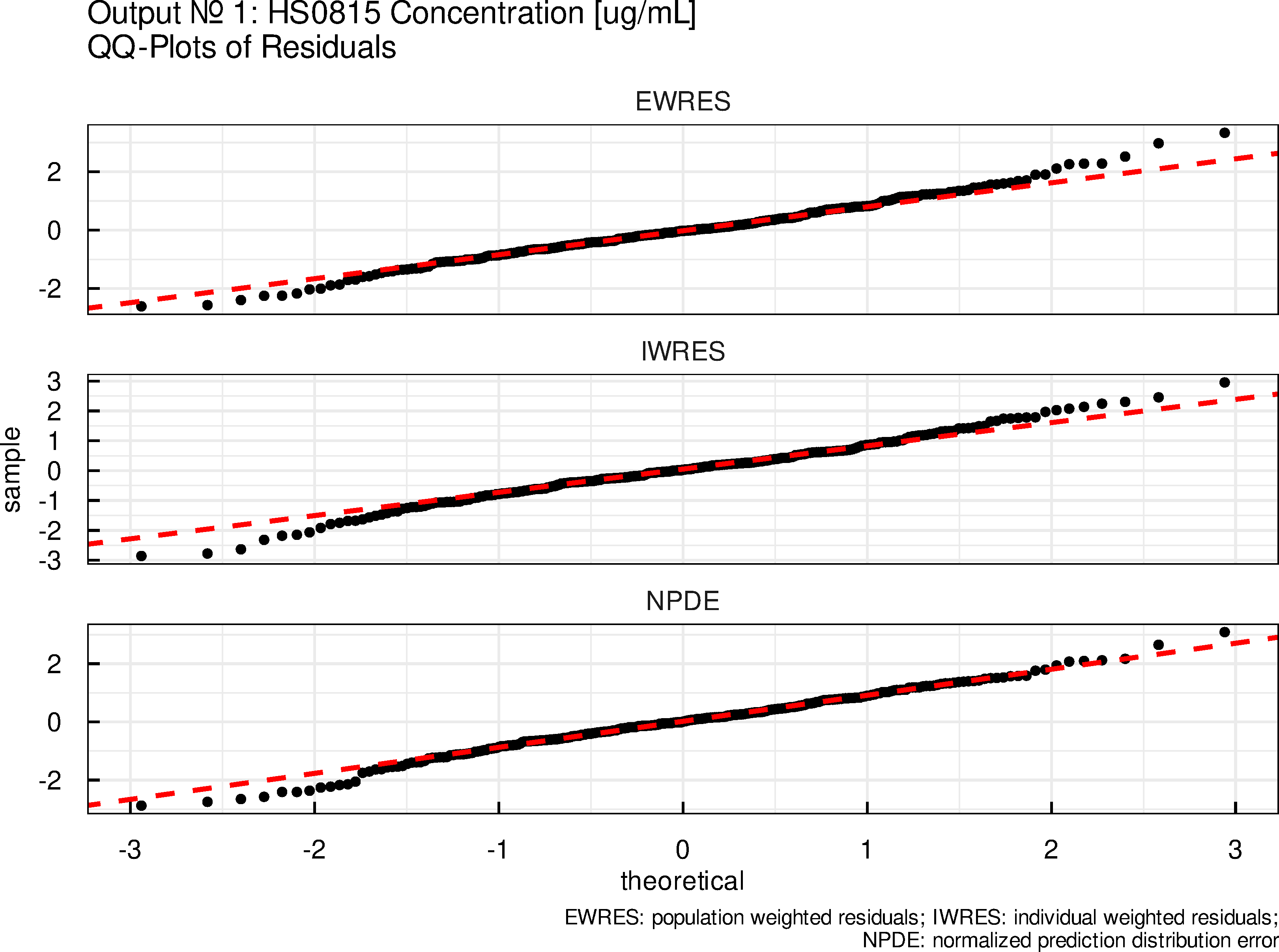
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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
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../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_OUTPUT\_1\_Cc/03\_GOF\_Plots.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
Page 7

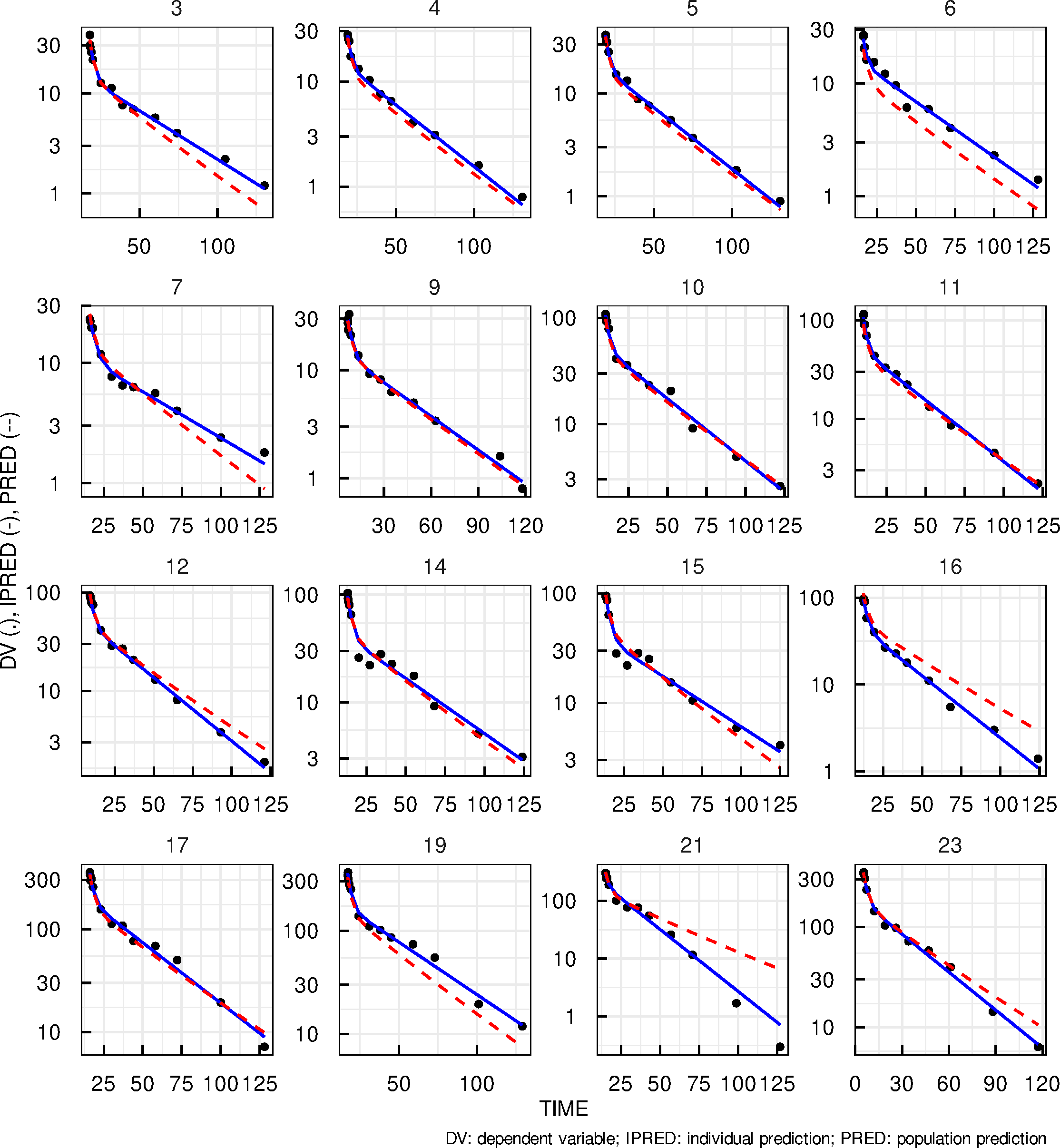


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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
Page 8

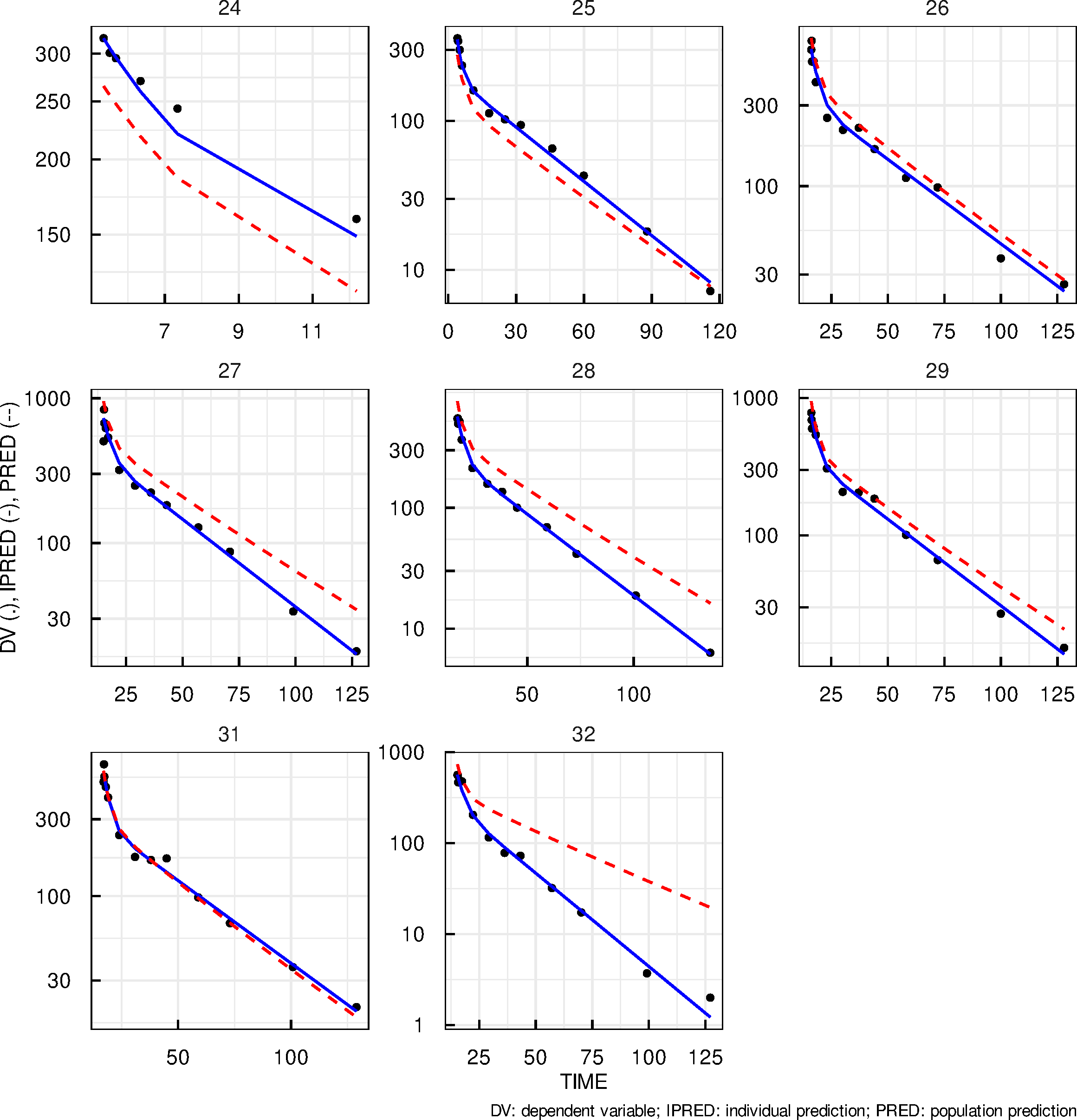


../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_OUTPUT\_1\_Cc/03\_GOF\_Plots.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:36  
Page 9

Figure Individual fits - log axis

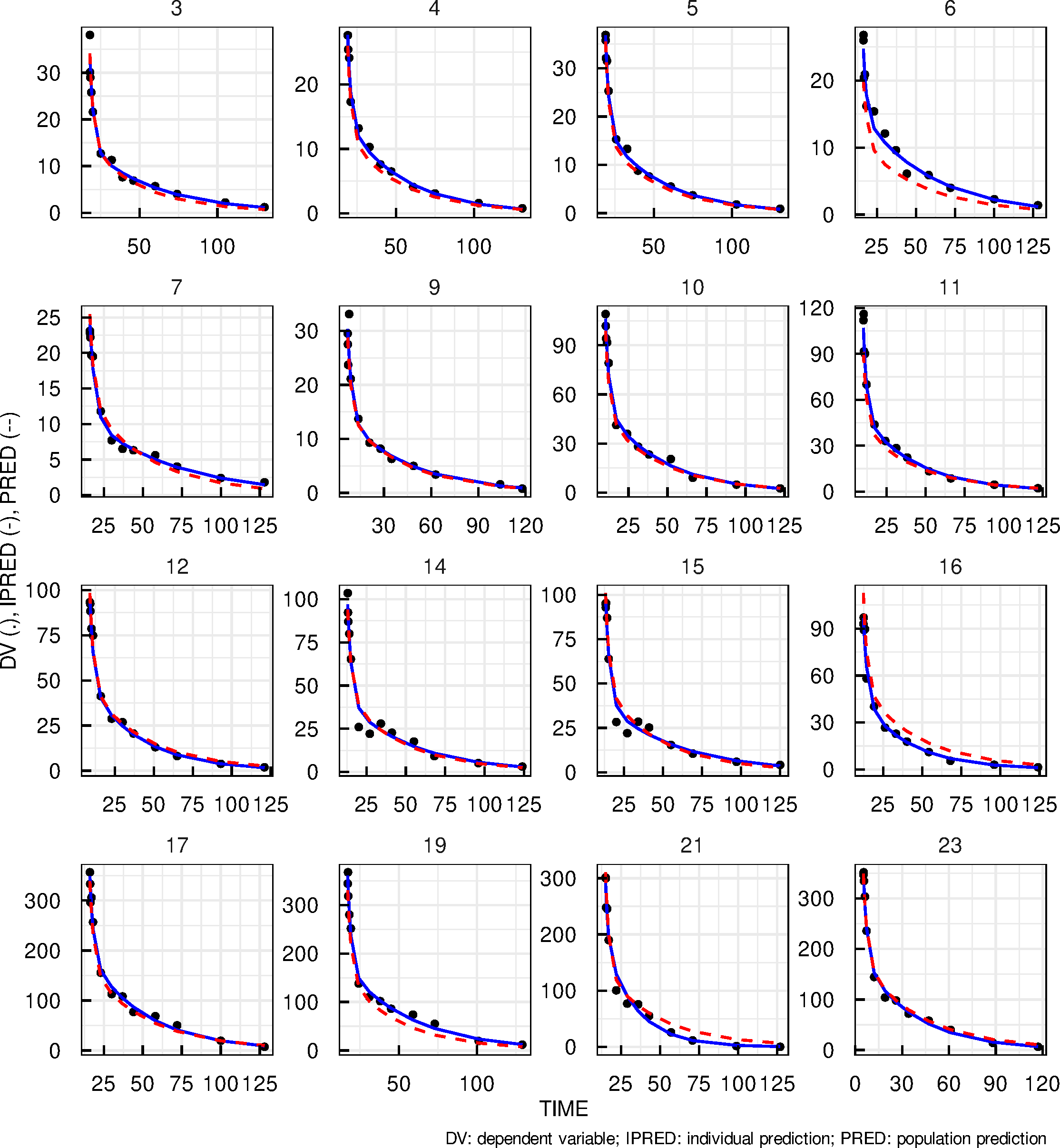


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2023-09-11 15:19:34  
Page 1

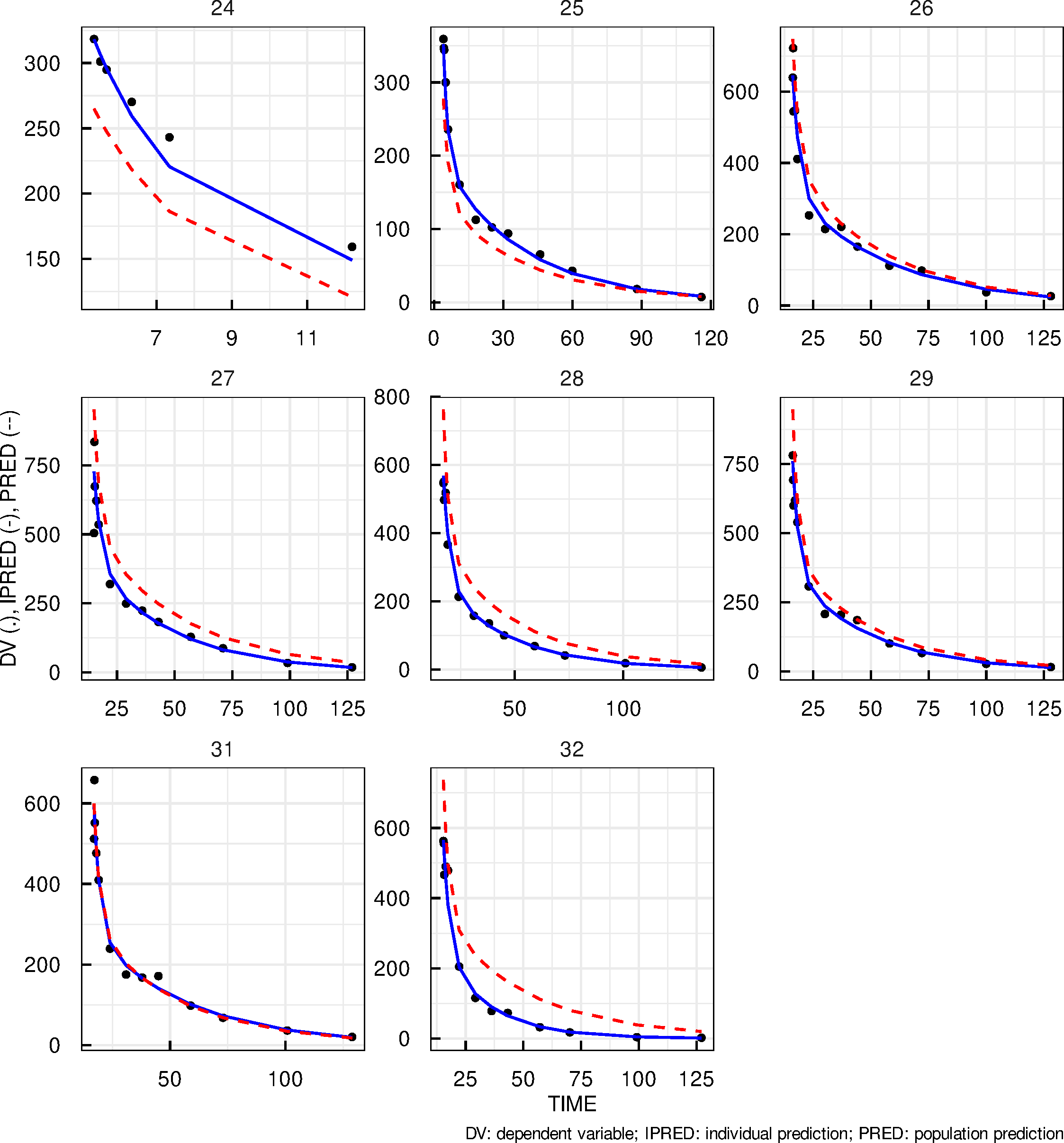


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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:34  
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Figure Individual fits - linear axis

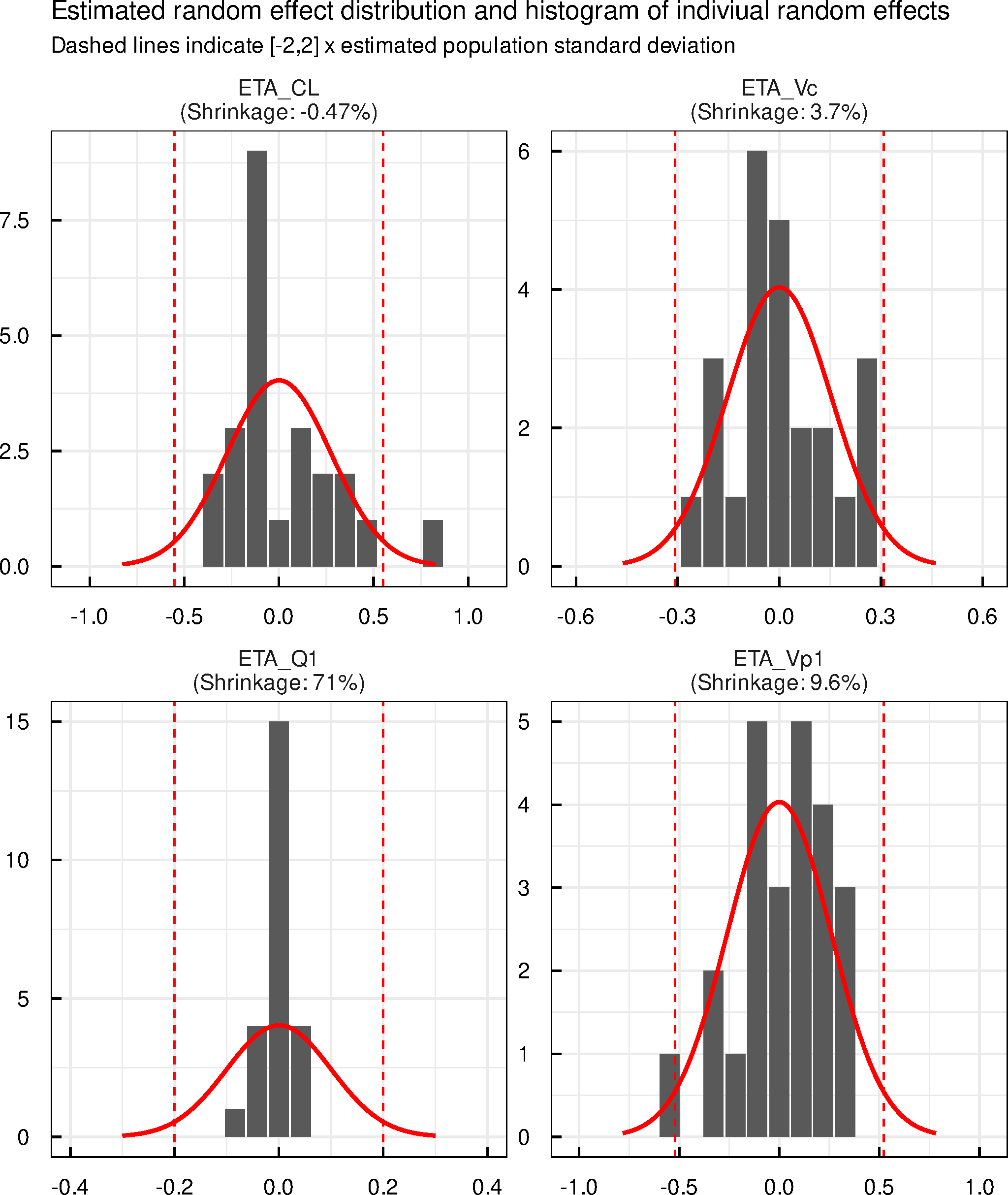


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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:33  
Page 1

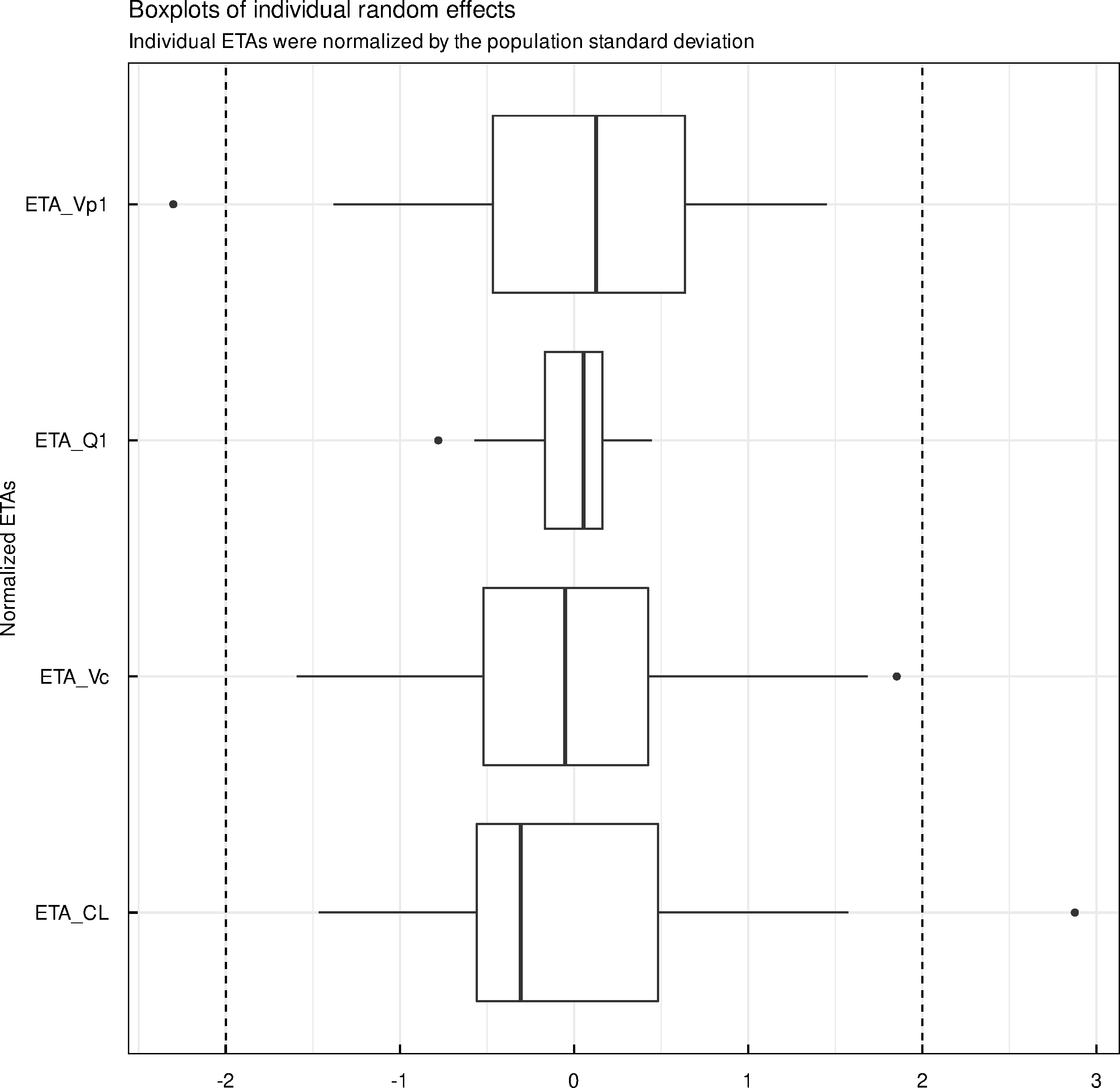


../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_OUTPUT\_1\_Cc/01\_Individual\_Fits\_LinearY.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:33  
Page 2

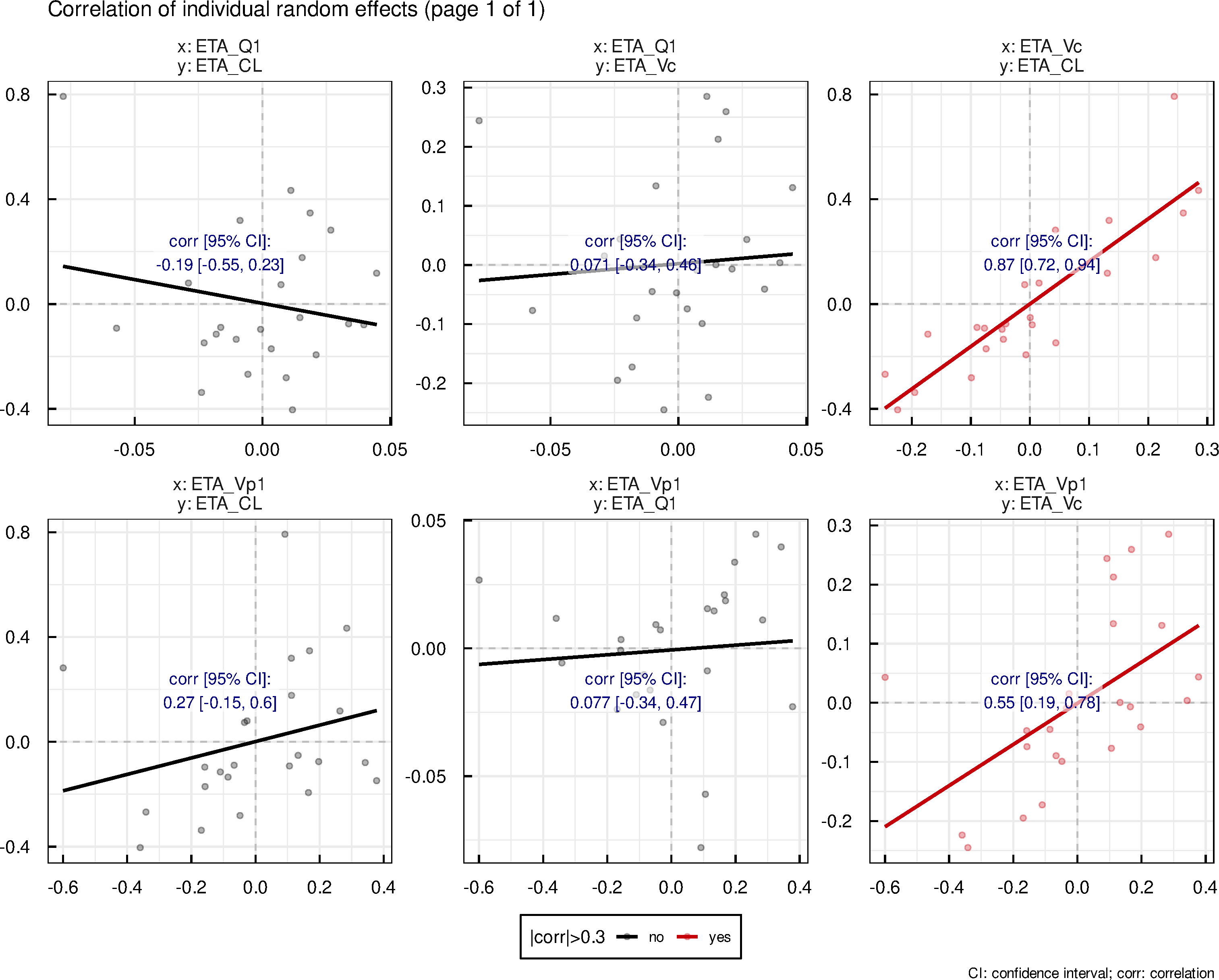
Figure Random effects



../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/01\_Random\_Effects.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:29  
Page 1

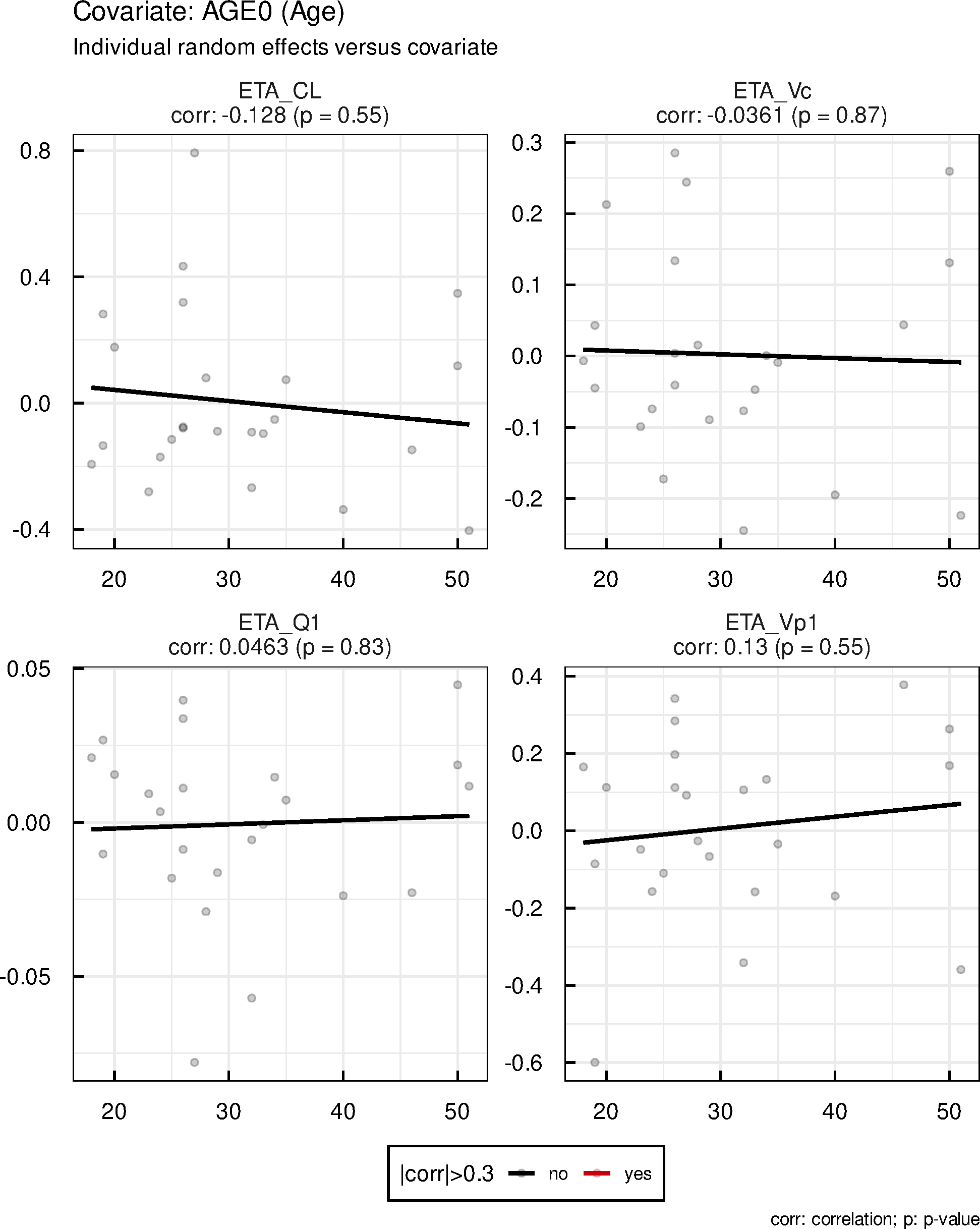


../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/01\_Random\_Effects.pdf  
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2023-09-11 15:19:29  
Page 2

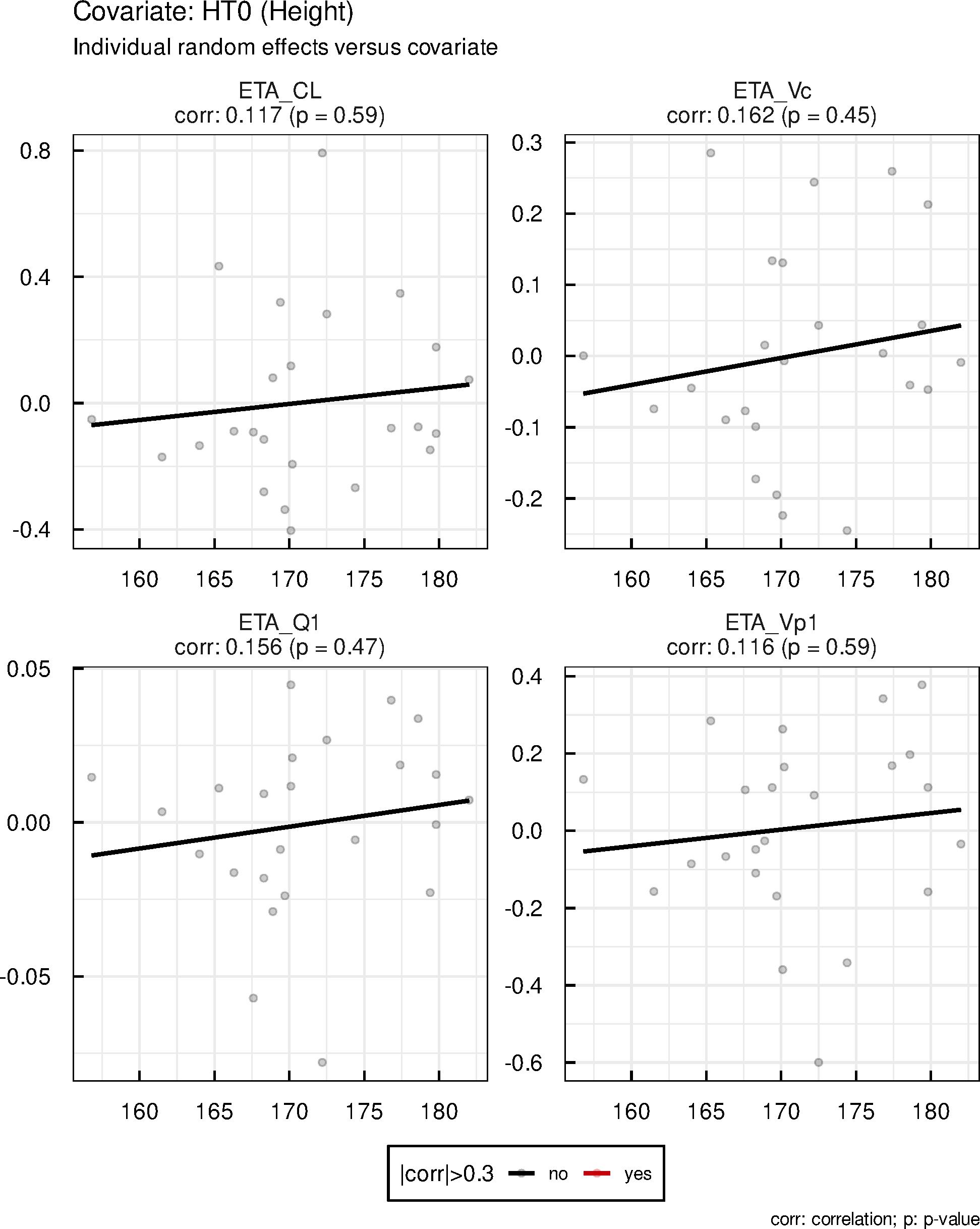


../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/01\_Random\_Effects.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:29  
Page 3

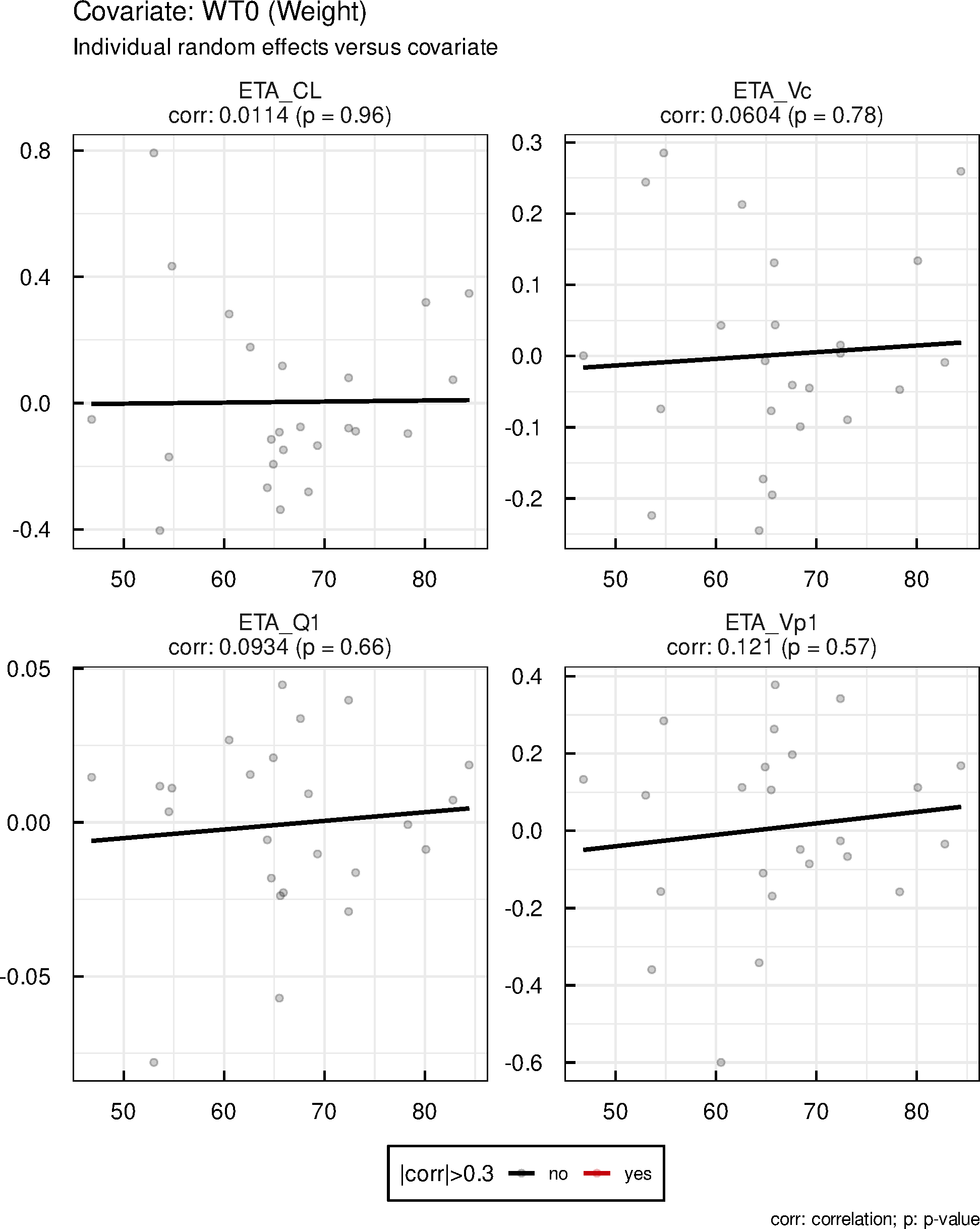
Figure Random effects versus covariates



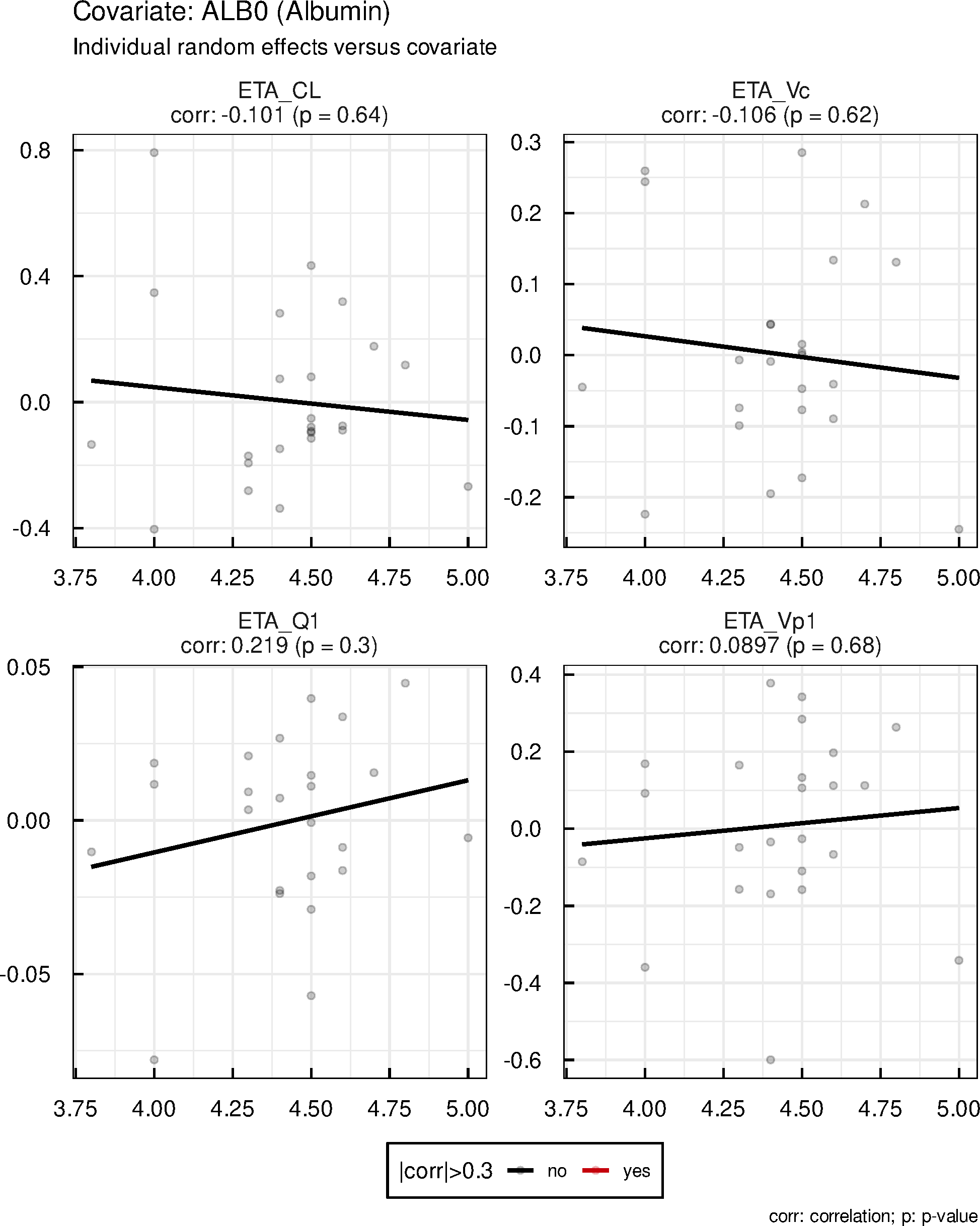
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2023-09-11 15:19:31  
Page 1



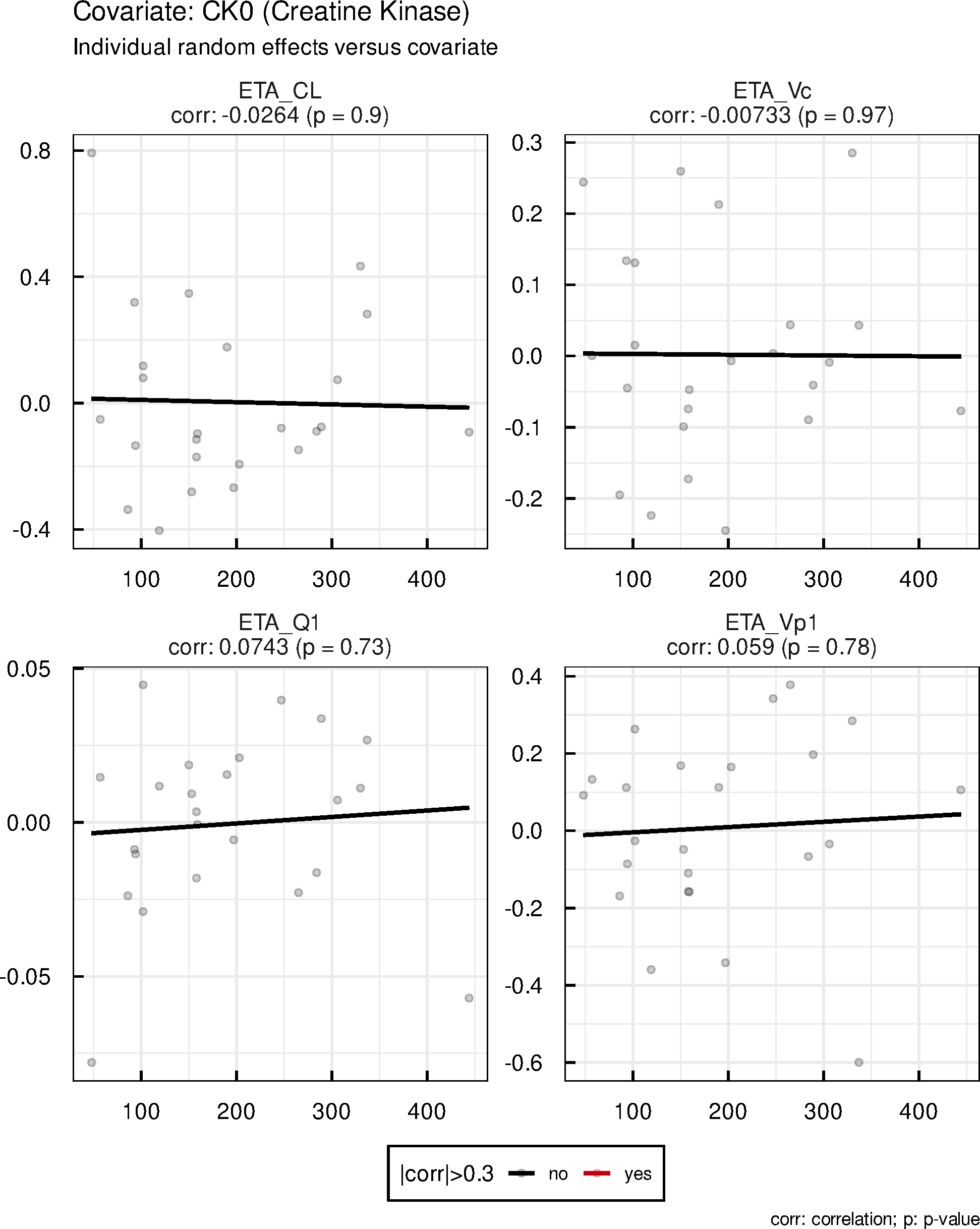
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SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:31  
Page 2



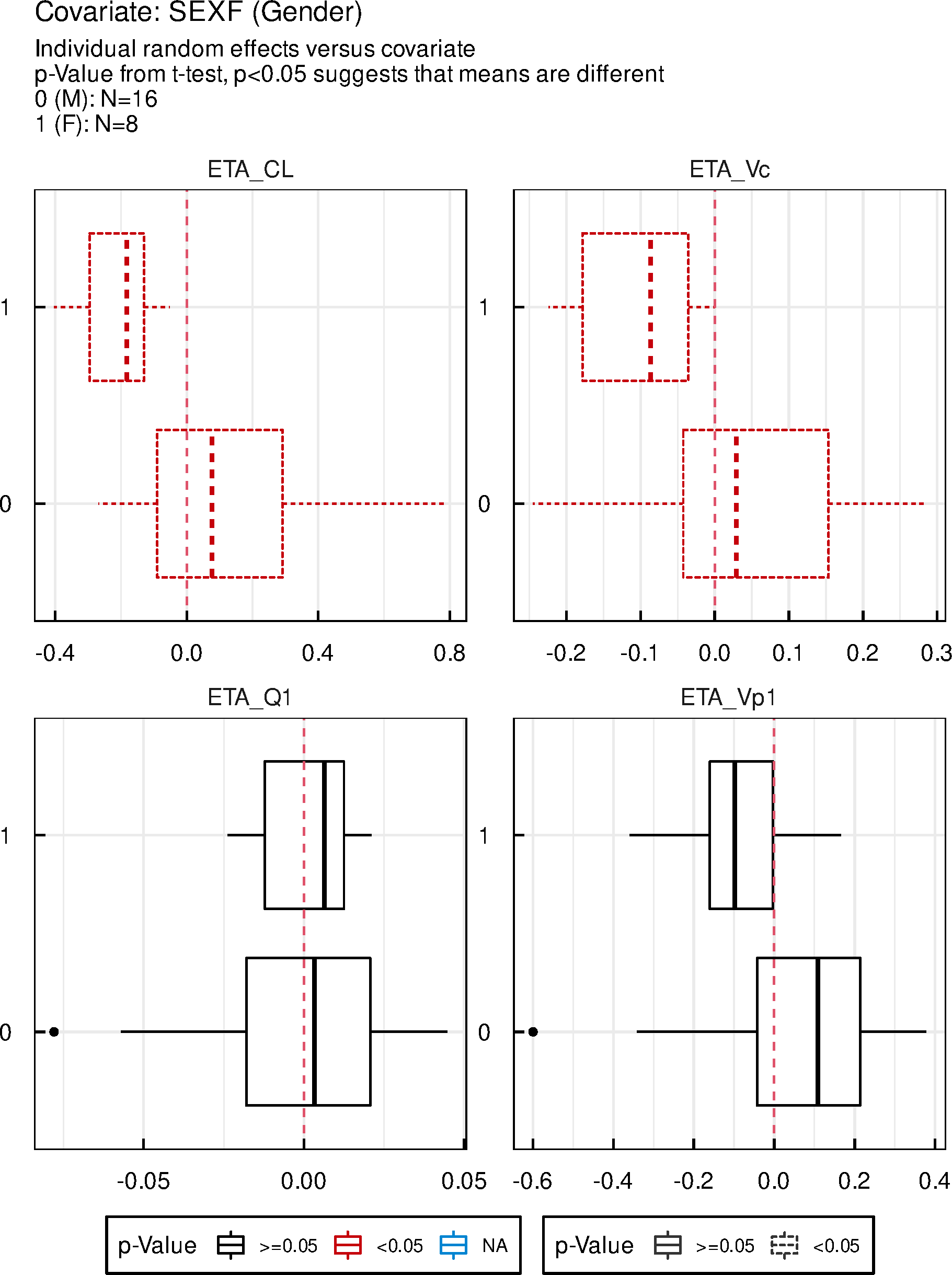
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2023-09-11 15:19:31  
Page 3



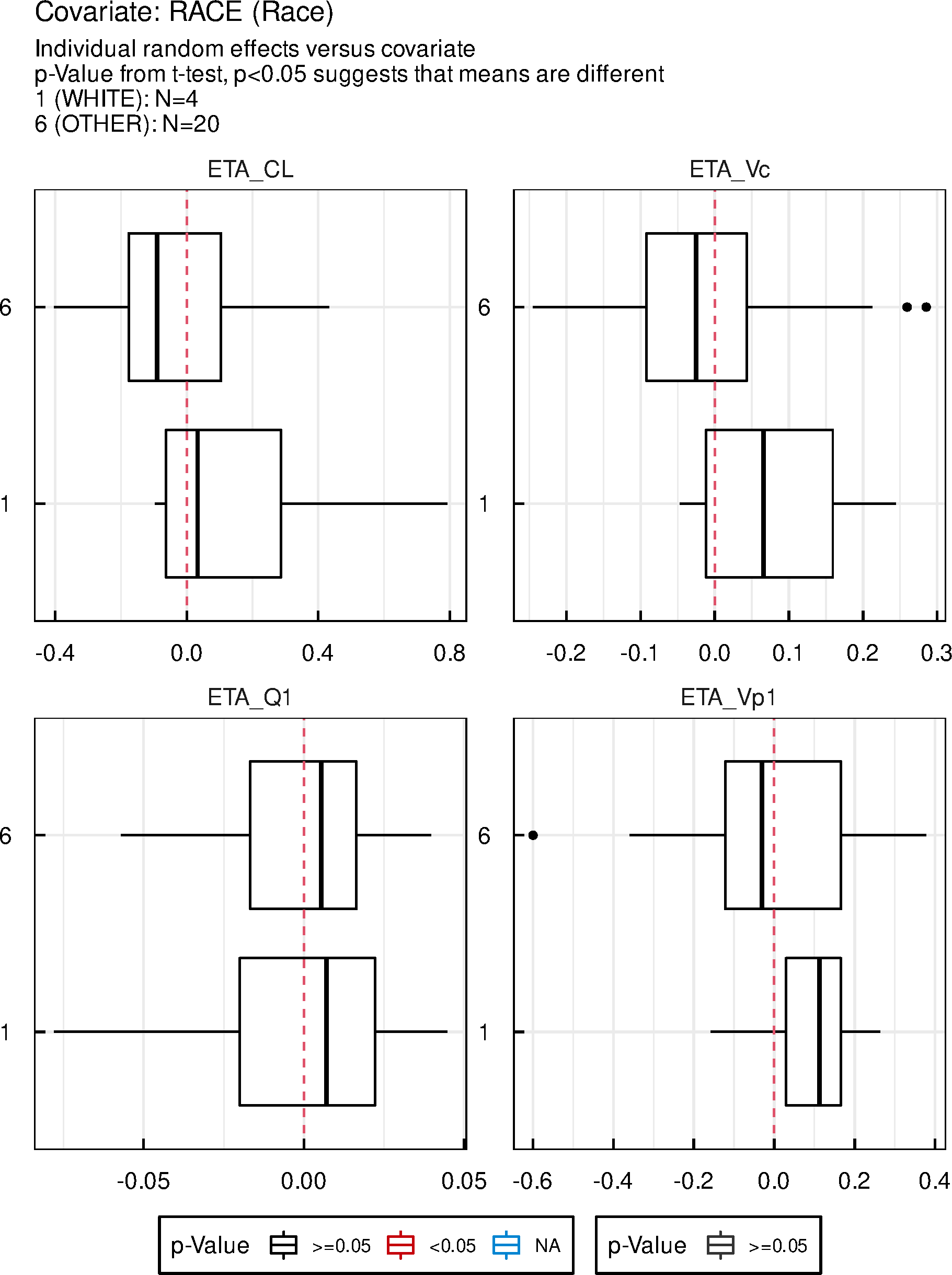
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2023-09-11 15:19:31  
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../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/02\_ETAs\_vs\_COVs.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:31  
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../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/02\_ETAs\_vs\_COVs.pdf  
SCRIPT\_25\_PK\_covariance.R  
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../Models/04\_covariance\_modeling/MODELCOR01/RESULTS/GOF\_GENERAL/02\_ETAs\_vs\_COVs.pdf  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:19:31  
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# Final Model

###### Text Final model NONMEM control file

../Models/04\_covariance\_modeling/MODELCOR01/project.nmctl  
SCRIPT\_25\_PK\_covariance.R  
2023-09-11 15:18:54

; NONMEM project generated with IQRtools  
  
; ==PROJECT HEADER START===================================================  
; COMMENT = 'CL/Vc'  
; TOOL = 'NONMEM'  
; TOOLVERSION = 'NM751'  
; FILE = 'project.nmctl'  
; METHOD = 'ITS,SAEM,IMP'  
; DATA = './dataNLME\_RATEfix.csv'  
; DOSINGTYPES = 'INFUSION'  
; TK0NAMES = 'NA'  
; COVNAMES = 'AGE0,HT0,WT0,ALB0,CK0'  
; CATNAMES = 'SEXF,RACE'  
; REGRESSIONNAMES = ''  
; OUTPUTS = 'Cc'  
; ERRORMODELS = 'absrel'  
; ERRORNAMES = 'error\_ADD1,error\_PROP1'  
; PARAMNAMES = 'CL,Vc,Q1,Vp1'  
; PARAMTRANS = 'exp(phi),exp(phi),exp(phi),exp(phi)'  
; PARAMINVTRANS = 'log(psi),log(psi),log(psi),log(psi)'  
; COVARIATENAMES = 'AGE0,HT0,WT0,ALB0,CK0,SEXF,RACE'  
; COVARIATESUSED = 'AGE0'  
; BETACOVNAMES = 'beta\_Vc(AGE0)'  
; BETACOVTRANS = 'log(cov/27.5)'  
; BETACATNAMES = ''  
; BETACATREFERENCE = ''  
; BETACATCATEGORIES = ''  
; THETANAMES = 'CL,Vc,Q1,Vp1,beta\_Vc(AGE0),error\_ADD1,error\_PROP1'  
; THETAESTIMATE = '1,1,1,1,1,1,1'  
; ETANAMES = 'omega(CL),omega(Vc),omega(Q1),omega(Vp1)'  
; ETAESTIMATE = '1,1,2,1'  
; CORRELATIONNAMES = 'corr(CL,Vc)'  
; CORRESTIMATE = '1'  
; IOVOCCASIONS = ''  
; IOVPARAMETERS = ''  
; IOVETANAMES = ''  
; IOVETAINDICES = ''  
; IOVETANAMESALL = ''  
; IOVETAINDICESALL = ''  
; NROBSERVATIONS = '305'  
; NRPARAM\_ESTIMATED = '11'  
; RESIDUAL\_NAMES\_USED = 'XPRED,XRES,XWRES'  
; RESIDUAL\_NAMES\_ORIG = 'EPRED,ERES,EWRES'  
; ==PROJECT HEADER END=====================================================  
  
$SIZES LIM1=353  
$SIZES LIM2=353  
$SIZES LIM6=353  
$SIZES LTH=7  
$SIZES PD=46  
$SIZES PC=7  
  
$PROBLEM MODELCOR01  
  
; Linear 2 compartmental distribution model  
; Dose: mg  
; Concentrations: ug/mL  
; Time: days  
  
$DATA ./dataNLME\_RATEfix.csv  
 IGNORE=@  
  
$INPUT SKIP SKIP SKIP ID SKIP SKIP SKIP SKIP TIME2 TIME TAD SKIP YTYPE SKIP  
 SKIP DV SKIP SKIP CENS MDV EVID AMT CMT II ADDL SKIP TINF RATE SKIP SKIP  
 SKIP SKIP SKIP SKIP AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
  
$SUBROUTINE ADVAN3 TRANS1  
  
$PK  
; Parameters  
  
 Tlag1 = 0  
  
; MU Referencing  
 MU\_1 = THETA(1) ; CL  
 MU\_2 = THETA(2) + THETA(5)\*log(AGE0/27.5) ; Vc  
 MU\_3 = THETA(3) ; Q1  
 MU\_4 = THETA(4) ; Vp1  
  
; MU+ETA  
 T\_CL = MU\_1 + ETA(1)  
 T\_Vc = MU\_2 + ETA(2)  
 T\_Q1 = MU\_3 + ETA(3)  
 T\_Vp1 = MU\_4 + ETA(4)  
  
; Parameter transformations  
 CL = EXP(T\_CL)  
 Vc = EXP(T\_Vc)  
 Q1 = EXP(T\_Q1)  
 Vp1 = EXP(T\_Vp1)  
  
; Dosing compartments info  
 F1 = 1; Ac  
  
  
 D1 = TINF ; TINF used if RATE=-2. If RATE=0 Bolus is made  
  
; Define TIMEOFFSET  
 TIMEOFFSET = TIME-TIME2  
  
; ADVAN parameters  
 K12 = Q1/Vc  
 K21 = Q1/Vp1  
 K = -(-Q1/Vc - CL/Vc)-(Q1/Vc)  
  
$ERROR  
; DEL to prevent numerical issues  
 DEL = 1.0E-30  
  
; States  
 Ac = A(1)  
 Ap1 = A(2)  
  
; Variables  
 Cc = Ac/Vc  
  
; Just to avoid a NONMEM warning  
 Y = 0  
 IPRED = 0  
 IRES = 0  
 W = 0  
 IWRES = 0  
  
; Error model OUTPUT1 / Cc  
 IF(YTYPE.EQ.1) THEN  
 IPRED = Cc  
 IRES = DV - IPRED  
 W = SQRT(THETA(6)\*\*2 + (THETA(7)\*IPRED)\*\*2)  
 IWRES = IRES/(ABS(W)+DEL)  
 Y = IPRED + W\*ERR(1)  
 ENDIF  
  
 IF(COMACT==1) THEN  
 PREDV = IPRED  
 RESV = IRES  
 WRESV = IWRES  
 ENDIF  
  
; Assign variables to report in tables  
 ETA\_CL = ETA(1)  
 ETA\_Vc = ETA(2)  
 ETA\_Q1 = ETA(3)  
 ETA\_Vp1 = ETA(4)  
  
$THETA  
; Model parameters  
 -0.693147 ; 1 log(CL) (0.5)  
 1.09861 ; 2 log(Vc) (3)  
 -0.693147 ; 3 log(Q1) (0.5)  
 1.09861 ; 4 log(Vp1) (3)  
  
; Covariate model parameters  
 0.1 ; 5 beta\_Vc(AGE0)  
  
; Error model parameters  
 0.2 ; 6 Absolute / Additive error OUTPUT1  
 0.3 ; 7 Relative / Proportional error OUTPUT1  
  
$OMEGA STANDARD CORRELATION BLOCK(2)  
 0.3 ; 1 CL  
 0.1 0.3 ; 2 Vc  
  
$OMEGA  
 0.1 STANDARD FIX ; 3 Q1  
 0.3 STANDARD ; 4 Vp1  
  
$SIGMA  
 1 FIX  
  
$ESTIMATION METHOD=ITS INTERACTION NOABORT NITER=10 SIGDIGITS=3 SIGL=9 PRINT=1  
 ETASTYPE=1  
  
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 NITER=10 MAPITER=0 SIGDIGITS=3 SIGL=9 PRINT=1 MUM=MMMMNNN  
 SEED=123456 ETASTYPE=1  
  
$COVARIANCE UNCONDITIONAL MATRIX=S PRINT=E  
  
$TABLE ID TIME TIME2 TAD YTYPE MDV EVID CENS DV IPRED IRES IWRES NPDE  
 EPRED=XPRED ERES=XRES EWRES=XWRES AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
 NOPRINT ONEHEADER NOAPPEND FILE=project.pred FORMAT=s1PG15.6  
 ESAMPLE=1000 SEED=123456  
  
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 ONEHEADER FIRSTONLY NOAPPEND FILE=project.eta FORMAT=s1PG15.6  
  
$TABLE ID CL Vc Q1 Vp1 AGE0 HT0 WT0 ALB0 CK0 SEXF RACE NOPRINT ONEHEADER  
 FIRSTONLY NOAPPEND FILE=project.indiv FORMAT=s1PG15.6

###### Text Final model NONMEM output file

Mon 11 Sep 2023 03:18:54 PM CEST  
; NONMEM project generated with IQRtools  
  
; ==PROJECT HEADER START===================================================  
; COMMENT = 'CL/Vc'  
; TOOL = 'NONMEM'  
; TOOLVERSION = 'NM751'  
; FILE = 'project.nmctl'  
; METHOD = 'ITS,SAEM,IMP'  
; DATA = './dataNLME\_RATEfix.csv'  
; DOSINGTYPES = 'INFUSION'  
; TK0NAMES = 'NA'  
; COVNAMES = 'AGE0,HT0,WT0,ALB0,CK0'  
; CATNAMES = 'SEXF,RACE'  
; REGRESSIONNAMES = ''  
; OUTPUTS = 'Cc'  
; ERRORMODELS = 'absrel'  
; ERRORNAMES = 'error\_ADD1,error\_PROP1'  
; PARAMNAMES = 'CL,Vc,Q1,Vp1'  
; PARAMTRANS = 'exp(phi),exp(phi),exp(phi),exp(phi)'  
; PARAMINVTRANS = 'log(psi),log(psi),log(psi),log(psi)'  
; COVARIATENAMES = 'AGE0,HT0,WT0,ALB0,CK0,SEXF,RACE'  
; COVARIATESUSED = 'AGE0'  
; BETACOVNAMES = 'beta\_Vc(AGE0)'  
; BETACOVTRANS = 'log(cov/27.5)'  
; BETACATNAMES = ''  
; BETACATREFERENCE = ''  
; BETACATCATEGORIES = ''  
; THETANAMES = 'CL,Vc,Q1,Vp1,beta\_Vc(AGE0),error\_ADD1,error\_PROP1'  
; THETAESTIMATE = '1,1,1,1,1,1,1'  
; ETANAMES = 'omega(CL),omega(Vc),omega(Q1),omega(Vp1)'  
; ETAESTIMATE = '1,1,2,1'  
; CORRELATIONNAMES = 'corr(CL,Vc)'  
; CORRESTIMATE = '1'  
; IOVOCCASIONS = ''  
; IOVPARAMETERS = ''  
; IOVETANAMES = ''  
; IOVETAINDICES = ''  
; IOVETANAMESALL = ''  
; IOVETAINDICESALL = ''  
; NROBSERVATIONS = '305'  
; NRPARAM\_ESTIMATED = '11'  
; RESIDUAL\_NAMES\_USED = 'XPRED,XRES,XWRES'  
; RESIDUAL\_NAMES\_ORIG = 'EPRED,ERES,EWRES'  
; ==PROJECT HEADER END=====================================================  
  
$SIZES LIM1=353  
$SIZES LIM2=353  
$SIZES LIM6=353  
$SIZES LTH=7  
$SIZES PD=46  
$SIZES PC=7  
  
$PROBLEM MODELCOR01  
  
; Linear 2 compartmental distribution model  
; Dose: mg  
; Concentrations: ug/mL  
; Time: days  
  
$DATA ./dataNLME\_RATEfix.csv  
 IGNORE=@  
  
$INPUT SKIP SKIP SKIP ID SKIP SKIP SKIP SKIP TIME2 TIME TAD SKIP YTYPE SKIP  
 SKIP DV SKIP SKIP CENS MDV EVID AMT CMT II ADDL SKIP TINF RATE SKIP SKIP  
 SKIP SKIP SKIP SKIP AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
  
$SUBROUTINE ADVAN3 TRANS1  
  
$PK  
; Parameters  
  
 Tlag1 = 0  
  
; MU Referencing  
 MU\_1 = THETA(1) ; CL  
 MU\_2 = THETA(2) + THETA(5)\*log(AGE0/27.5) ; Vc  
 MU\_3 = THETA(3) ; Q1  
 MU\_4 = THETA(4) ; Vp1  
  
; MU+ETA  
 T\_CL = MU\_1 + ETA(1)  
 T\_Vc = MU\_2 + ETA(2)  
 T\_Q1 = MU\_3 + ETA(3)  
 T\_Vp1 = MU\_4 + ETA(4)  
  
; Parameter transformations  
 CL = EXP(T\_CL)  
 Vc = EXP(T\_Vc)  
 Q1 = EXP(T\_Q1)  
 Vp1 = EXP(T\_Vp1)  
  
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 D1 = TINF ; TINF used if RATE=-2. If RATE=0 Bolus is made  
  
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; ADVAN parameters  
 K12 = Q1/Vc  
 K21 = Q1/Vp1  
 K = -(-Q1/Vc - CL/Vc)-(Q1/Vc)  
  
$ERROR  
; DEL to prevent numerical issues  
 DEL = 1.0E-30  
  
; States  
 Ac = A(1)  
 Ap1 = A(2)  
  
; Variables  
 Cc = Ac/Vc  
  
; Just to avoid a NONMEM warning  
 Y = 0  
 IPRED = 0  
 IRES = 0  
 W = 0  
 IWRES = 0  
  
; Error model OUTPUT1 / Cc  
 IF(YTYPE.EQ.1) THEN  
 IPRED = Cc  
 IRES = DV - IPRED  
 W = SQRT(THETA(6)\*\*2 + (THETA(7)\*IPRED)\*\*2)  
 IWRES = IRES/(ABS(W)+DEL)  
 Y = IPRED + W\*ERR(1)  
 ENDIF  
  
 IF(COMACT==1) THEN  
 PREDV = IPRED  
 RESV = IRES  
 WRESV = IWRES  
 ENDIF  
  
; Assign variables to report in tables  
 ETA\_CL = ETA(1)  
 ETA\_Vc = ETA(2)  
 ETA\_Q1 = ETA(3)  
 ETA\_Vp1 = ETA(4)  
  
$THETA  
; Model parameters  
 -0.693147 ; 1 log(CL) (0.5)  
 1.09861 ; 2 log(Vc) (3)  
 -0.693147 ; 3 log(Q1) (0.5)  
 1.09861 ; 4 log(Vp1) (3)  
  
; Covariate model parameters  
 0.1 ; 5 beta\_Vc(AGE0)  
  
; Error model parameters  
 0.2 ; 6 Absolute / Additive error OUTPUT1  
 0.3 ; 7 Relative / Proportional error OUTPUT1  
  
$OMEGA STANDARD CORRELATION BLOCK(2)  
 0.3 ; 1 CL  
 0.1 0.3 ; 2 Vc  
  
$OMEGA  
 0.1 STANDARD FIX ; 3 Q1  
 0.3 STANDARD ; 4 Vp1  
  
$SIGMA  
 1 FIX  
  
$ESTIMATION METHOD=ITS INTERACTION NOABORT NITER=10 SIGDIGITS=3 SIGL=9 PRINT=1  
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 MUM=MMMMNNN ETASTYPE=1  
  
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 NITER=10 MAPITER=0 SIGDIGITS=3 SIGL=9 PRINT=1 MUM=MMMMNNN  
 SEED=123456 ETASTYPE=1  
  
$COVARIANCE UNCONDITIONAL MATRIX=S PRINT=E  
  
$TABLE ID TIME TIME2 TAD YTYPE MDV EVID CENS DV IPRED IRES IWRES NPDE  
 EPRED=XPRED ERES=XRES EWRES=XWRES AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
 NOPRINT ONEHEADER NOAPPEND FILE=project.pred FORMAT=s1PG15.6  
 ESAMPLE=1000 SEED=123456  
  
$TABLE ID ETA\_CL ETA\_Vc ETA\_Q1 ETA\_Vp1 AGE0 HT0 WT0 ALB0 CK0 SEXF RACE NOPRINT  
 ONEHEADER FIRSTONLY NOAPPEND FILE=project.eta FORMAT=s1PG15.6  
  
$TABLE ID CL Vc Q1 Vp1 AGE0 HT0 WT0 ALB0 CK0 SEXF RACE NOPRINT ONEHEADER  
 FIRSTONLY NOAPPEND FILE=project.indiv FORMAT=s1PG15.6  
  
  
  
NM-TRAN MESSAGES  
   
 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1  
   
 (WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.  
   
 (WARNING 26) THE DERIVATIVE OF THE ABSOLUTE VALUE OF A RANDOM VARIABLE IS  
 BEING COMPUTED. IF THE ABSOLUTE VALUE AFFECTS THE VALUE OF THE OBJECTIVE  
 FUNCTION, THE USER SHOULD ENSURE THAT THE RANDOM VARIABLE IS ALWAYS  
 POSITIVE OR ALWAYS NEGATIVE.  
  
 (MU\_WARNING 26) DATA ITEM(S) USED IN DEFINITION OF MU\_(S) SHOULD BE CONSTANT FOR INDIV. REC.:  
 AGE0  
   
Note: Analytical 2nd Derivatives are constructed in FSUBS but are never used.  
 You may insert $ABBR DERIV2=NO after the first $PROB to save FSUBS construction and compilation time  
   
  
License Registered to: IntiQuan GmbH  
Expiration Date: 14 JAN 2024  
Current Date: 11 SEP 2023  
Days until program expires : 128  
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.5.1  
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN  
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,  
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION  
 PERFORMED BY NOUS INFOSYSTEMS.  
  
 PROBLEM NO.: 1  
 MODELCOR01  
0DATA CHECKOUT RUN: NO  
 DATA SET LOCATED ON UNIT NO.: 2  
 THIS UNIT TO BE REWOUND: NO  
 NO. OF DATA RECS IN DATA SET: 353  
 NO. OF DATA ITEMS IN DATA SET: 22  
 ID DATA ITEM IS DATA ITEM NO.: 1  
 DEP VARIABLE IS DATA ITEM NO.: 6  
 MDV DATA ITEM IS DATA ITEM NO.: 8  
0INDICES PASSED TO SUBROUTINE PRED:  
 9 3 10 15 0 12 11 0 0 0 13  
0LABELS FOR DATA ITEMS:  
 ID TIME2 TIME TAD YTYPE DV CENS MDV EVID AMT CMT II ADDL TINF RATE AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
0LABELS FOR SPECIAL ITEMS:  
 PRED RES WRES  
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:  
 CL Vc Q1 Vp1 IPRED IRES IWRES ETA\_CL ETA\_Vc ETA\_Q1 ETA\_Vp1  
0FORMAT FOR DATA:  
 (E2.0,E20.0,E16.0,E20.0,E1.0,E5.0,3E1.0,E5.0,3E1.0/E18.0,8E5.0)  
  
 TOT. NO. OF OBS RECS: 305  
 TOT. NO. OF INDIVIDUALS: 24  
0LENGTH OF THETA: 7  
0DEFAULT THETA BOUNDARY TEST OMITTED: NO  
0OMEGA HAS BLOCK FORM:  
 1  
 1 1  
 0 0 2  
 0 0 0 3  
0DEFAULT OMEGA BOUNDARY TEST OMITTED: NO  
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1  
0DEFAULT SIGMA BOUNDARY TEST OMITTED: NO  
0INITIAL ESTIMATE OF THETA:  
 -0.6931E+00 0.1099E+01 -0.6931E+00 0.1099E+01 0.1000E+00 0.2000E+00 0.3000E+00  
0INITIAL ESTIMATE OF OMEGA:  
 BLOCK SET NO. BLOCK FIXED  
 1 NO  
 0.9000E-01  
 0.9000E-02 0.9000E-01  
 2 YES  
 0.1000E-01  
 3 NO  
 0.9000E-01  
0INITIAL ESTIMATE OF SIGMA:  
 0.1000E+01  
0SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE  
0COVARIANCE STEP OMITTED: NO  
 R MATRIX SUBSTITUTED: NO  
 S MATRIX SUBSTITUTED: YES  
 EIGENVLS. PRINTED: YES  
 SPECIAL COMPUTATION: NO  
 COMPRESSED FORMAT: NO  
 GRADIENT METHOD USED: NOSLOW  
 SIGDIGITS ETAHAT (SIGLO): -1  
 SIGDIGITS GRADIENTS (SIGL): -1  
 EXCLUDE COV FOR FOCE (NOFCOV): NO  
 Cholesky Transposition of R Matrix (CHOLROFF):0  
 KNUTHSUMOFF: -1  
 RESUME COV ANALYSIS (RESUME): NO  
 SIR SAMPLE SIZE (SIRSAMPLE):  
 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1  
 PRECONDTIONING CYCLES (PRECOND): 0  
 PRECONDTIONING TYPES (PRECONDS): TOS  
 FORCED PRECONDTIONING CYCLES (PFCOND):0  
 PRECONDTIONING TYPE (PRETYPE): 0  
 FORCED POS. DEFINITE SETTING DURING PRECONDITIONING: (FPOSDEF):0  
 SIMPLE POS. DEFINITE SETTING: (POSDEF):-1  
0TABLES STEP OMITTED: NO  
 NO. OF TABLES: 3  
 SEED NUMBER (SEED): 123456  
 NPDTYPE: 0  
 INTERPTYPE: 0  
 RANMETHOD: 3U  
 MC SAMPLES (ESAMPLE): 1000  
 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE  
0-- TABLE 1 --  
0RECORDS ONLY: ALL  
04 COLUMNS APPENDED: NO  
 PRINTED: NO  
 HEADER: YES  
 FILE TO BE FORWARDED: NO  
 FORMAT: s1PG15.6  
 IDFORMAT:  
 LFORMAT:  
 RFORMAT:  
 FIXED\_EFFECT\_ETAS:  
0USER-CHOSEN ITEMS:  
 ID TIME TIME2 TAD YTYPE MDV EVID CENS DV IPRED IRES IWRES NPDE XPRED XRES XWRES AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
0-- TABLE 2 --  
0RECORDS ONLY: FIRSTONLY  
04 COLUMNS APPENDED: NO  
 PRINTED: NO  
 HEADER: YES  
 FILE TO BE FORWARDED: NO  
 FORMAT: s1PG15.6  
 IDFORMAT:  
 LFORMAT:  
 RFORMAT:  
 FIXED\_EFFECT\_ETAS:  
0USER-CHOSEN ITEMS:  
 ID ETA\_CL ETA\_Vc ETA\_Q1 ETA\_Vp1 AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
0-- TABLE 3 --  
0RECORDS ONLY: FIRSTONLY  
04 COLUMNS APPENDED: NO  
 PRINTED: NO  
 HEADER: YES  
 FILE TO BE FORWARDED: NO  
 FORMAT: s1PG15.6  
 IDFORMAT:  
 LFORMAT:  
 RFORMAT:  
 FIXED\_EFFECT\_ETAS:  
0USER-CHOSEN ITEMS:  
 ID CL Vc Q1 Vp1 AGE0 HT0 WT0 ALB0 CK0 SEXF RACE  
1DOUBLE PRECISION PREDPP VERSION 7.5.1  
  
 TWO COMPARTMENT MODEL (ADVAN3)  
0MAXIMUM NO. OF BASIC PK PARAMETERS: 4  
0BASIC PK PARAMETERS (AFTER TRANSLATION):  
 BASIC PK PARAMETER NO. 1: ELIMINATION RATE (K)  
 BASIC PK PARAMETER NO. 2: CENTRAL-TO-PERIPH. RATE (K12)  
 BASIC PK PARAMETER NO. 3: PERIPH.-TO-CENTRAL RATE (K21)  
0COMPARTMENT ATTRIBUTES  
 COMPT. NO. FUNCTION INITIAL ON/OFF DOSE DEFAULT DEFAULT  
 STATUS ALLOWED ALLOWED FOR DOSE FOR OBS.  
 1 CENTRAL ON NO YES YES YES  
 2 PERIPH. ON NO YES NO NO  
 3 OUTPUT OFF YES NO NO NO  
1  
 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG  
 COMPT. NO. INDICES  
 SCALE BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB  
 FRACTION RATE DURATION LAG  
 1 \* 5 \* 6 \*  
 2 \* \* \* \* \*  
 3 \* - - - -  
 - PARAMETER IS NOT ALLOWED FOR THIS MODEL  
 \* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;  
 WILL DEFAULT TO ONE IF APPLICABLE  
0DATA ITEM INDICES USED BY PRED ARE:  
 EVENT ID DATA ITEM IS DATA ITEM NO.: 9  
 TIME DATA ITEM IS DATA ITEM NO.: 3  
 DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 10  
 DOSE RATE DATA ITEM IS DATA ITEM NO.: 15  
 INTERVAL DATA ITEM IS DATA ITEM NO.: 12  
 ADDL. DOSES DATA ITEM IS DATA ITEM NO.: 13  
 COMPT. NO. DATA ITEM IS DATA ITEM NO.: 11  
  
0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.  
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.  
0ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.  
0ERROR SUBROUTINE INDICATES THAT DERIVATIVES OF COMPARTMENT AMOUNTS ARE USED.  
  
 #PARA: PARAFILE=template.pnm, PROTOCOL=MPI, NODES= 4  
  
1  
  
  
 #TBLN: 1  
 #METH: Iterative Two Stage  
  
 ESTIMATION STEP OMITTED: NO  
 ANALYSIS TYPE: POPULATION  
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0  
 GRADIENT METHOD USED: NOSLOW  
 CONDITIONAL ESTIMATES USED: YES  
 CENTERED ETA: NO  
 EPS-ETA INTERACTION: YES  
 LAPLACIAN OBJ. FUNC.: NO  
 NO. OF FUNCT. EVALS. ALLOWED: 840  
 NO. OF SIG. FIGURES REQUIRED: 3  
 INTERMEDIATE PRINTOUT: YES  
 ESTIMATE OUTPUT TO MSF: NO  
 ABORT WITH PRED EXIT CODE 1: NO  
 IND. OBJ. FUNC. VALUES SORTED: NO  
 NUMERICAL DERIVATIVE  
 FILE REQUEST (NUMDER): NONE  
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0  
 ETA HESSIAN EVALUATION METHOD (ETADER): 0  
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0  
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 9  
 GRADIENT SIGDIGITS OF  
 FIXED EFFECTS PARAMETERS (SIGL): 9  
 NOPRIOR SETTING (NOPRIOR): 0  
 NOCOV SETTING (NOCOV): OFF  
 DERCONT SETTING (DERCONT): OFF  
 FINAL ETA RE-EVALUATION (FNLETA): 1  
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS  
 IN SHRINKAGE (ETASTYPE): YES  
 NON-INFL. ETA CORRECTION (NONINFETA): 0  
 RAW OUTPUT FILE (FILE): project.ext  
 EXCLUDE TITLE (NOTITLE): NO  
 EXCLUDE COLUMN LABELS (NOLABEL): NO  
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5  
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL  
 KNUTHSUMOFF: 0  
 INCLUDE LNTWOPI: NO  
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO  
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO  
 EM OR BAYESIAN METHOD USED: ITERATIVE TWO STAGE (ITS)  
 MU MODELING PATTERN (MUM):  
 GRADIENT/GIBBS PATTERN (GRD):  
 AUTOMATIC SETTING FEATURE (AUTO): 0  
 CONVERGENCE TYPE (CTYPE): 0  
 ITERATIONS (NITER): 10  
 ANNEAL SETTING (CONSTRAIN): 1  
  
  
 THE FOLLOWING LABELS ARE EQUIVALENT  
 PRED=PREDI  
 RES=RESI  
 WRES=WRESI  
 IWRS=IWRESI  
 IPRD=IPREDI  
 IRS=IRESI  
 EPRED=XPRED  
 ERES=XRES  
 EWRES=XWRES  
  
 EM/BAYES SETUP:  
 THETAS THAT ARE MU MODELED:  
 1 2 3 4 5  
 THETAS THAT ARE SIGMA-LIKE:  
   
  
 MONITORING OF SEARCH:  
  
 iteration 0 OBJ= 2083.7091039515408  
 iteration 1 OBJ= 1690.9247190167057  
 iteration 2 OBJ= 1628.2629374879759  
 iteration 3 OBJ= 1577.9931414676391  
 iteration 4 OBJ= 1533.3565474960183  
 iteration 5 OBJ= 1497.2217718017957  
 iteration 6 OBJ= 1480.1591821272320  
 iteration 7 OBJ= 1476.8258363161958  
 iteration 8 OBJ= 1475.6671944063996  
 iteration 9 OBJ= 1475.2028307816749  
 iteration 10 OBJ= 1474.9914616768208  
  
 #TERM:  
 OPTIMIZATION WAS NOT TESTED FOR CONVERGENCE  
  
  
 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,  
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.  
  
 ETABAR: -4.7519E-04 1.9350E-04 -2.2653E-03 7.8233E-06  
 SE: 5.5370E-02 2.9713E-02 5.6952E-03 4.5651E-02  
 N: 24 24 24 24  
  
 P VAL.: 9.9315E-01 9.9480E-01 6.9081E-01 9.9986E-01  
  
 ETASHRINKSD(%%) 1.5654E+00 5.1051E+00 7.2099E+01 1.0941E+01  
 ETASHRINKVR(%%) 3.1063E+00 9.9496E+00 9.2216E+01 2.0684E+01  
 EBVSHRINKSD(%%) 1.6522E+00 4.9441E+00 7.3906E+01 1.2241E+01  
 EBVSHRINKVR(%%) 3.2770E+00 9.6438E+00 9.3191E+01 2.2983E+01  
 RELATIVEINF(%%) 8.8718E+01 6.0497E+01 5.6511E+00 7.1660E+01  
 EPSSHRINKSD(%%) 1.0836E+01  
 EPSSHRINKVR(%%) 2.0499E+01  
  
   
 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 305  
 N\*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 560.55250525485030   
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1474.9914616768208   
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 2035.5439669316711   
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT  
   
 TOTAL EFFECTIVE ETAS (NIND\*NETA): 96  
   
 #TERE:  
 Elapsed estimation time in seconds: 0.87  
 Elapsed covariance time in seconds: 0.04  
1  
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 #OBJT:\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL VALUE OF OBJECTIVE FUNCTION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
  
  
  
  
 #OBJV:\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* 1474.991 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL PARAMETER ESTIMATE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
  
 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 -1.91E+00 9.94E-01 -6.98E-01 8.49E-01 3.54E-01 3.61E-01 1.08E-01  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 7.59E-02  
   
 ETA2  
+ 3.52E-02 2.35E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-02  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 6.31E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 2.76E-01  
   
 ETA2  
+ 8.34E-01 1.53E-01  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-01  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 2.51E-01  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STANDARD ERROR OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
  
 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 1.05E-01 5.51E-02 1.25E-01 1.05E-01 8.05E-02 1.41E-01 6.47E-03  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 3.18E-02  
   
 ETA2  
+ 1.80E-02 1.03E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 0.00E+00  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 3.52E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 0.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 5.77E-02  
   
 ETA2  
+ 1.42E-01 3.35E-02  
   
 ETA3  
+ ......... ......... .........  
   
 ETA4  
+ ......... ......... ......... 7.01E-02  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ .........  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.10E-02  
   
 TH 2  
+ 4.21E-03 3.03E-03  
   
 TH 3  
+ 1.43E-03 -1.75E-03 1.55E-02  
   
 TH 4  
+ -2.36E-03 -3.28E-03 1.19E-04 1.10E-02  
   
 TH 5  
+ -2.04E-03 -7.42E-04 1.98E-03 -2.70E-03 6.48E-03  
   
 TH 6  
+ -9.17E-03 -2.42E-03 -5.78E-03 3.02E-03 -6.92E-04 1.98E-02  
   
 TH 7  
+ 1.71E-04 9.74E-05 -1.16E-04 -1.98E-04 4.52E-06 -4.22E-04 4.19E-05  
   
 OM11  
+ -1.02E-03 -4.36E-04 1.08E-03 -6.13E-05 6.56E-04 -6.53E-04 5.39E-06 1.01E-03  
   
 OM12  
+ -6.24E-04 -2.41E-04 1.63E-04 8.95E-05 2.87E-04 8.81E-05 3.92E-06 5.32E-04 3.25E-04  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.97E-04 -1.32E-04 8.06E-05 -7.07E-06 2.09E-04 -4.65E-05 1.31E-05 2.46E-04 1.61E-04 0.00E+00 0.00E+00 1.05E-04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 9.46E-04 1.74E-04 -8.91E-04 1.60E-03 -1.18E-03 -1.37E-03 -2.03E-05 -6.48E-05 -4.20E-05 0.00E+00 0.00E+00 -5.71E-05  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.24E-03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... ......... ......... .........  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* CORRELATION MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.05E-01  
   
 TH 2  
+ 7.27E-01 5.51E-02  
   
 TH 3  
+ 1.09E-01 -2.55E-01 1.25E-01  
   
 TH 4  
+ -2.14E-01 -5.66E-01 9.06E-03 1.05E-01  
   
 TH 5  
+ -2.41E-01 -1.67E-01 1.97E-01 -3.19E-01 8.05E-02  
   
 TH 6  
+ -6.19E-01 -3.12E-01 -3.29E-01 2.04E-01 -6.11E-02 1.41E-01  
   
 TH 7  
+ 2.51E-01 2.73E-01 -1.44E-01 -2.91E-01 8.67E-03 -4.62E-01 6.47E-03  
   
 OM11  
+ -3.05E-01 -2.49E-01 2.73E-01 -1.83E-02 2.56E-01 -1.46E-01 2.62E-02 3.18E-02  
   
 OM12  
+ -3.29E-01 -2.42E-01 7.25E-02 4.73E-02 1.98E-01 3.47E-02 3.36E-02 9.27E-01 1.80E-02  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.75E-01 -2.34E-01 6.30E-02 -6.56E-03 2.53E-01 -3.22E-02 1.97E-01 7.54E-01 8.71E-01 0.00E+00 0.00E+00 1.03E-02  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 2.56E-01 8.96E-02 -2.03E-01 4.34E-01 -4.15E-01 -2.75E-01 -8.90E-02 -5.78E-02 -6.61E-02 0.00E+00 0.00E+00 -1.58E-01  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 3.52E-02  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* INVERSE COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 7.67E+02  
   
 TH 2  
+ -1.02E+03 2.25E+03  
   
 TH 3  
+ -1.90E+02 3.12E+02 1.88E+02  
   
 TH 4  
+ -1.68E+02 5.42E+02 1.95E+01 3.02E+02  
   
 TH 5  
+ 5.56E+01 6.36E+01 7.35E+00 6.09E+01 2.46E+02  
   
 TH 6  
+ 3.33E+02 -3.09E+02 -1.43E+01 -7.10E+01 6.47E+01 3.15E+02  
   
 TH 7  
+ 9.99E+02 -9.19E+02 7.57E+02 3.82E+00 7.35E+02 1.99E+03 4.82E+04  
   
 OM11  
+ 2.46E+03 -2.12E+03 -1.11E+03 3.63E+01 7.02E+01 1.71E+03 4.71E+03 2.44E+04  
   
 OM12  
+ -3.89E+03 2.87E+03 1.89E+03 -2.00E+02 -5.43E+01 -3.11E+03 -3.75E+03 -4.59E+04 1.02E+05  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ 1.20E+03 1.74E+00 -5.82E+02 9.38E+01 -2.99E+02 1.27E+03 -8.98E+03 1.84E+04 -5.82E+04 0.00E+00 0.00E+00 6.25E+04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 OM44  
+ 1.27E+02 -3.24E+02 1.93E+02 -3.45E+02 1.80E+02 3.55E+02 3.29E+03 1.73E+02 -1.01E+03 0.00E+00 0.00E+00 1.39E+03  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.99E+03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* ITERATIVE TWO STAGE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* EIGENVALUES OF COR MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 1 2 3 4 5 6 7 8 9 10 11  
   
 1.55E-02 7.03E-02 1.62E-01 1.78E-01 3.59E-01 6.40E-01 8.24E-01 1.33E+00 1.71E+00 2.41E+00 3.30E+00  
   
1  
  
  
 #TBLN: 2  
 #METH: Stochastic Approximation Expectation-Maximization  
  
 ESTIMATION STEP OMITTED: NO  
 ANALYSIS TYPE: POPULATION  
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0  
 GRADIENT METHOD USED: NOSLOW  
 CONDITIONAL ESTIMATES USED: YES  
 CENTERED ETA: NO  
 EPS-ETA INTERACTION: YES  
 LAPLACIAN OBJ. FUNC.: NO  
 NO. OF FUNCT. EVALS. ALLOWED: 840  
 NO. OF SIG. FIGURES REQUIRED: 3  
 INTERMEDIATE PRINTOUT: YES  
 ESTIMATE OUTPUT TO MSF: NO  
 ABORT WITH PRED EXIT CODE 1: NO  
 IND. OBJ. FUNC. VALUES SORTED: NO  
 NUMERICAL DERIVATIVE  
 FILE REQUEST (NUMDER): NONE  
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0  
 ETA HESSIAN EVALUATION METHOD (ETADER): 0  
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0  
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 9  
 GRADIENT SIGDIGITS OF  
 FIXED EFFECTS PARAMETERS (SIGL): 9  
 NOPRIOR SETTING (NOPRIOR): 0  
 NOCOV SETTING (NOCOV): OFF  
 DERCONT SETTING (DERCONT): OFF  
 FINAL ETA RE-EVALUATION (FNLETA): 1  
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS  
 IN SHRINKAGE (ETASTYPE): YES  
 NON-INFL. ETA CORRECTION (NONINFETA): 0  
 RAW OUTPUT FILE (FILE): project.ext  
 EXCLUDE TITLE (NOTITLE): NO  
 EXCLUDE COLUMN LABELS (NOLABEL): NO  
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5  
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL  
 KNUTHSUMOFF: 0  
 INCLUDE LNTWOPI: NO  
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO  
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO  
 EM OR BAYESIAN METHOD USED: STOCHASTIC APPROXIMATION EXPECTATION MAXIMIZATION (SAEM)  
 MU MODELING PATTERN (MUM): MMMMNNN  
 GRADIENT/GIBBS PATTERN (GRD):  
 AUTOMATIC SETTING FEATURE (AUTO): 0  
 CONVERGENCE TYPE (CTYPE): 0  
 BURN-IN ITERATIONS (NBURN): 500  
 FIRST ITERATION FOR MAP (MAPITERS): NO  
 ITERATIONS (NITER): 200  
 ANNEAL SETTING (CONSTRAIN): 1  
 STARTING SEED FOR MC METHODS (SEED): 123456  
 MC SAMPLES PER SUBJECT (ISAMPLE): 3  
 RANDOM SAMPLING METHOD (RANMETHOD): 3UP  
 EXPECTATION ONLY (EONLY): 0  
 PROPOSAL DENSITY SCALING RANGE  
 (ISCALE\_MIN, ISCALE\_MAX): 1.000000000000000E-06 ,1000000.00000000  
 SAMPLE ACCEPTANCE RATE (IACCEPT): 0.400000000000000  
 METROPOLIS HASTINGS SAMPLING FOR INDIVIDUAL ETAS:  
 SAMPLES FOR GLOBAL SEARCH KERNEL (ISAMPLE\_M1): 2  
 SAMPLES FOR NEIGHBOR SEARCH KERNEL (ISAMPLE\_M1A): 0  
 SAMPLES FOR MASS/IMP/POST. MATRIX SEARCH (ISAMPLE\_M1B): 2  
 SAMPLES FOR LOCAL SEARCH KERNEL (ISAMPLE\_M2): 2  
 SAMPLES FOR LOCAL UNIVARIATE KERNEL (ISAMPLE\_M3): 2  
 PWR. WT. MASS/IMP/POST MATRIX ACCUM. FOR ETAS (IKAPPA): 1.00000000000000  
 MASS/IMP./POST. MATRIX REFRESH SETTING (MASSRESET): -1  
  
  
 THE FOLLOWING LABELS ARE EQUIVALENT  
 PRED=PREDI  
 RES=RESI  
 WRES=WRESI  
 IWRS=IWRESI  
 IPRD=IPREDI  
 IRS=IRESI  
 EPRED=XPRED  
 ERES=XRES  
 EWRES=XWRES  
  
 EM/BAYES SETUP:  
 THETAS THAT ARE MU MODELED:  
 1 2 3 4  
 THETAS THAT ARE SIGMA-LIKE:  
   
  
 MONITORING OF SEARCH:  
  
 Stochastic/Burn-in Mode  
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 #TERM:  
 STOCHASTIC PORTION WAS NOT TESTED FOR CONVERGENCE  
 REDUCED STOCHASTIC PORTION WAS COMPLETED  
  
 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,  
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.  
  
 ETABAR: -1.1548E-05 -5.0991E-05 -8.3203E-06 2.0965E-05  
 SE: 5.5354E-02 2.9858E-02 5.7925E-03 4.7098E-02  
 N: 24 24 24 24  
  
 P VAL.: 9.9983E-01 9.9864E-01 9.9885E-01 9.9964E-01  
  
 ETASHRINKSD(%%) 1.6012E+00 4.9468E+00 7.1623E+01 1.1450E+01  
 ETASHRINKVR(%%) 3.1769E+00 9.6489E+00 9.1947E+01 2.1588E+01  
 EBVSHRINKSD(%%) 1.6051E+00 4.9859E+00 6.8147E+01 1.1412E+01  
 EBVSHRINKVR(%%) 3.1844E+00 9.7232E+00 8.9854E+01 2.1522E+01  
 RELATIVEINF(%%) 9.0231E+01 6.4360E+01 8.8760E+00 7.4517E+01  
 EPSSHRINKSD(%%) 1.0088E+01  
 EPSSHRINKVR(%%) 1.9157E+01  
  
   
 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 305  
 N\*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 560.55250525485030   
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1012.8018950474830   
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 1573.3544003023333   
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT  
   
 TOTAL EFFECTIVE ETAS (NIND\*NETA): 96  
 NIND\*NETA\*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 176.43619837529715   
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1012.8018950474830   
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 1189.2380934227801   
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT  
   
 #TERE:  
 Elapsed estimation time in seconds: 22.45  
 Elapsed covariance time in seconds: 0.02  
1  
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 #OBJT:\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL VALUE OF LIKELIHOOD FUNCTION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 #OBJV:\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* 1012.802 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL PARAMETER ESTIMATE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
  
 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 -1.92E+00 9.97E-01 -7.31E-01 8.33E-01 3.24E-01 3.22E-01 1.07E-01  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 7.60E-02  
   
 ETA2  
+ 3.48E-02 2.37E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-02  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 6.79E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 2.76E-01  
   
 ETA2  
+ 8.22E-01 1.54E-01  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-01  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 2.61E-01  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STANDARD ERROR OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
  
 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 1.10E-01 5.44E-02 1.13E-01 1.08E-01 7.79E-02 1.49E-01 6.35E-03  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 3.17E-02  
   
 ETA2  
+ 1.81E-02 1.02E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 0.00E+00  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 3.83E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 0.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 5.76E-02  
   
 ETA2  
+ 1.55E-01 3.30E-02  
   
 ETA3  
+ ......... ......... .........  
   
 ETA4  
+ ......... ......... ......... 7.35E-02  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ .........  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.21E-02  
   
 TH 2  
+ 4.41E-03 2.96E-03  
   
 TH 3  
+ 1.57E-03 -1.07E-03 1.29E-02  
   
 TH 4  
+ -2.58E-03 -3.33E-03 -3.24E-04 1.17E-02  
   
 TH 5  
+ -1.94E-03 -8.25E-04 1.24E-03 -2.06E-03 6.06E-03  
   
 TH 6  
+ -1.11E-02 -2.93E-03 -4.40E-03 2.82E-03 4.96E-04 2.22E-02  
   
 TH 7  
+ 2.27E-04 9.28E-05 -6.87E-05 -1.69E-04 -4.45E-05 -5.30E-04 4.03E-05  
   
 OM11  
+ -7.63E-04 -3.93E-04 8.51E-04 1.11E-04 4.52E-04 -1.01E-03 1.74E-05 1.01E-03  
   
 OM12  
+ -5.98E-04 -2.70E-04 1.27E-05 2.75E-04 1.89E-04 7.93E-05 3.15E-06 5.22E-04 3.29E-04  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.75E-04 -1.36E-04 -5.30E-05 1.03E-04 7.16E-05 -4.23E-05 1.26E-05 2.35E-04 1.60E-04 0.00E+00 0.00E+00 1.03E-04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 1.14E-03 1.39E-04 -8.16E-04 1.86E-03 -1.07E-03 -1.97E-03 -5.94E-06 9.80E-05 5.06E-05 0.00E+00 0.00E+00 1.03E-06  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.47E-03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... ......... ......... .........  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* CORRELATION MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.10E-01  
   
 TH 2  
+ 7.36E-01 5.44E-02  
   
 TH 3  
+ 1.26E-01 -1.73E-01 1.13E-01  
   
 TH 4  
+ -2.16E-01 -5.67E-01 -2.64E-02 1.08E-01  
   
 TH 5  
+ -2.26E-01 -1.95E-01 1.40E-01 -2.44E-01 7.79E-02  
   
 TH 6  
+ -6.74E-01 -3.61E-01 -2.61E-01 1.75E-01 4.27E-02 1.49E-01  
   
 TH 7  
+ 3.25E-01 2.69E-01 -9.54E-02 -2.46E-01 -9.01E-02 -5.61E-01 6.35E-03  
   
 OM11  
+ -2.18E-01 -2.27E-01 2.36E-01 3.23E-02 1.83E-01 -2.13E-01 8.65E-02 3.17E-02  
   
 OM12  
+ -2.99E-01 -2.73E-01 6.15E-03 1.41E-01 1.34E-01 2.93E-02 2.74E-02 9.06E-01 1.81E-02  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.45E-01 -2.46E-01 -4.60E-02 9.42E-02 9.05E-02 -2.79E-02 1.96E-01 7.29E-01 8.67E-01 0.00E+00 0.00E+00 1.02E-02  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 2.69E-01 6.68E-02 -1.88E-01 4.50E-01 -3.57E-01 -3.46E-01 -2.44E-02 8.06E-02 7.28E-02 0.00E+00 0.00E+00 2.64E-03  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 3.83E-02  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... ......... ......... .........  
   
1  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* INVERSE COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 7.35E+02  
   
 TH 2  
+ -9.63E+02 2.16E+03  
   
 TH 3  
+ -1.81E+02 2.88E+02 1.93E+02  
   
 TH 4  
+ -1.55E+02 5.05E+02 1.48E+01 2.77E+02  
   
 TH 5  
+ 1.32E+01 1.33E+02 1.69E+01 6.09E+01 2.37E+02  
   
 TH 6  
+ 3.88E+02 -3.60E+02 -4.11E+01 -7.06E+01 5.57E+01 3.96E+02  
   
 TH 7  
+ 1.08E+03 -8.32E+02 7.20E+02 -6.58E+01 7.91E+02 2.50E+03 5.64E+04  
   
 OM11  
+ 2.45E+03 -2.14E+03 -1.11E+03 5.05E+01 1.10E+02 2.11E+03 5.61E+03 2.29E+04  
   
 OM12  
+ -3.99E+03 3.10E+03 1.82E+03 -2.24E+02 -4.60E+02 -3.82E+03 -5.97E+03 -4.22E+04 9.26E+04  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ 1.35E+03 -1.45E+02 -4.15E+02 1.57E+02 3.81E+02 1.54E+03 -7.79E+03 1.63E+04 -5.29E+04 0.00E+00 0.00E+00 5.86E+04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 1.27E+02 -2.94E+02 1.73E+02 -3.19E+02 1.68E+02 3.74E+02 3.73E+03 4.77E+02 -1.75E+03 0.00E+00 0.00E+00 1.54E+03  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.78E+03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... ......... ......... .........  
   
1  
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STOCHASTIC APPROXIMATION EXPECTATION-MAXIMIZATION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* EIGENVALUES OF COR MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
   
  
 1 2 3 4 5 6 7 8 9 10 11  
   
 1.59E-02 7.38E-02 1.57E-01 1.84E-01 3.55E-01 7.12E-01 8.02E-01 1.25E+00 1.80E+00 2.46E+00 3.18E+00  
   
1  
  
  
 #TBLN: 3  
 #METH: Objective Function Evaluation by Importance Sampling  
  
 ESTIMATION STEP OMITTED: NO  
 ANALYSIS TYPE: POPULATION  
 NUMBER OF SADDLE POINT RESET ITERATIONS: 0  
 GRADIENT METHOD USED: NOSLOW  
 CONDITIONAL ESTIMATES USED: YES  
 CENTERED ETA: NO  
 EPS-ETA INTERACTION: YES  
 LAPLACIAN OBJ. FUNC.: NO  
 NO. OF FUNCT. EVALS. ALLOWED: 840  
 NO. OF SIG. FIGURES REQUIRED: 3  
 INTERMEDIATE PRINTOUT: YES  
 ESTIMATE OUTPUT TO MSF: NO  
 ABORT WITH PRED EXIT CODE 1: NO  
 IND. OBJ. FUNC. VALUES SORTED: NO  
 NUMERICAL DERIVATIVE  
 FILE REQUEST (NUMDER): NONE  
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0  
 ETA HESSIAN EVALUATION METHOD (ETADER): 0  
 INITIAL ETA FOR MAP ESTIMATION (MCETA): 0  
 SIGDIGITS FOR MAP ESTIMATION (SIGLO): 9  
 GRADIENT SIGDIGITS OF  
 FIXED EFFECTS PARAMETERS (SIGL): 9  
 NOPRIOR SETTING (NOPRIOR): 0  
 NOCOV SETTING (NOCOV): OFF  
 DERCONT SETTING (DERCONT): OFF  
 FINAL ETA RE-EVALUATION (FNLETA): 1  
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS  
 IN SHRINKAGE (ETASTYPE): YES  
 NON-INFL. ETA CORRECTION (NONINFETA): 0  
 RAW OUTPUT FILE (FILE): project.ext  
 EXCLUDE TITLE (NOTITLE): NO  
 EXCLUDE COLUMN LABELS (NOLABEL): NO  
 FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5  
 PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL  
 KNUTHSUMOFF: 0  
 INCLUDE LNTWOPI: NO  
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO  
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO  
 EM OR BAYESIAN METHOD USED: IMPORTANCE SAMPLING (IMP)  
 MU MODELING PATTERN (MUM): MMMMNNN  
 GRADIENT/GIBBS PATTERN (GRD):  
 AUTOMATIC SETTING FEATURE (AUTO): 0  
 CONVERGENCE TYPE (CTYPE): 0  
 ITERATIONS (NITER): 10  
 ANNEAL SETTING (CONSTRAIN): 1  
 STARTING SEED FOR MC METHODS (SEED): 123456  
 MC SAMPLES PER SUBJECT (ISAMPLE): 1000  
 RANDOM SAMPLING METHOD (RANMETHOD): 3UP  
 EXPECTATION ONLY (EONLY): 1  
 PROPOSAL DENSITY SCALING RANGE  
 (ISCALE\_MIN, ISCALE\_MAX): 0.100000000000000 ,10.0000000000000  
 SAMPLE ACCEPTANCE RATE (IACCEPT): 0.400000000000000  
 LONG TAIL SAMPLE ACCEPT. RATE (IACCEPTL): 0.00000000000000  
 T-DIST. PROPOSAL DENSITY (DF): 0  
 NO. ITERATIONS FOR MAP (MAPITER): 0  
 INTERVAL ITER. FOR MAP (MAPINTER): 0  
 MAP COVARIANCE/MODE SETTING (MAPCOV): 1  
 Gradient Quick Value (GRDQ): 0.00000000000000  
  
  
 THE FOLLOWING LABELS ARE EQUIVALENT  
 PRED=PREDI  
 RES=RESI  
 WRES=WRESI  
 IWRS=IWRESI  
 IPRD=IPREDI  
 IRS=IRESI  
 EPRED=XPRED  
 ERES=XRES  
 EWRES=XWRES  
  
 EM/BAYES SETUP:  
 THETAS THAT ARE MU MODELED:  
 1 2 3 4  
 THETAS THAT ARE SIGMA-LIKE:  
   
  
 MONITORING OF SEARCH:  
  
 iteration 0 OBJ= 1473.7646878024752 eff.= 1023. Smpl.= 1000. Fit.= 0.97890  
 iteration 1 OBJ= 1473.5956701347284 eff.= 391. Smpl.= 1000. Fit.= 0.89652  
 iteration 2 OBJ= 1473.7505940788687 eff.= 402. Smpl.= 1000. Fit.= 0.90086  
 iteration 3 OBJ= 1473.8146331306727 eff.= 399. Smpl.= 1000. Fit.= 0.90009  
 iteration 4 OBJ= 1473.6874776451975 eff.= 403. Smpl.= 1000. Fit.= 0.90023  
 iteration 5 OBJ= 1473.9349824970873 eff.= 396. Smpl.= 1000. Fit.= 0.89947  
 iteration 6 OBJ= 1473.6983375648881 eff.= 401. Smpl.= 1000. Fit.= 0.90003  
 iteration 7 OBJ= 1473.7283829822079 eff.= 407. Smpl.= 1000. Fit.= 0.90155  
 iteration 8 OBJ= 1473.9624458442429 eff.= 397. Smpl.= 1000. Fit.= 0.89975  
 iteration 9 OBJ= 1473.5974976001914 eff.= 395. Smpl.= 1000. Fit.= 0.89798  
 iteration 10 OBJ= 1473.7463202823099 eff.= 409. Smpl.= 1000. Fit.= 0.90156  
  
 #TERM:  
 EXPECTATION ONLY PROCESS WAS NOT TESTED FOR CONVERGENCE  
  
  
 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,  
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.  
  
 ETABAR: -7.8748E-04 4.8528E-04 5.3887E-05 -2.6416E-04  
 SE: 5.5377E-02 2.9620E-02 5.6193E-03 4.7234E-02  
 N: 24 24 24 24  
  
 P VAL.: 9.8865E-01 9.8693E-01 9.9235E-01 9.9554E-01  
  
 ETASHRINKSD(%%) 1.5598E+00 5.7068E+00 7.2471E+01 1.1194E+01  
 ETASHRINKVR(%%) 3.0953E+00 1.1088E+01 9.2422E+01 2.1135E+01  
 EBVSHRINKSD(%%) 1.5716E+00 4.9342E+00 7.3029E+01 1.1693E+01  
 EBVSHRINKVR(%%) 3.1186E+00 9.6250E+00 9.2726E+01 2.2018E+01  
 RELATIVEINF(%%) 8.8482E+01 6.0301E+01 5.8033E+00 7.1544E+01  
 EPSSHRINKSD(%%) 1.0008E+01  
 EPSSHRINKVR(%%) 1.9014E+01  
  
   
 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 305  
 N\*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 560.55250525485030   
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 1473.7463202823099   
 OBJECTIVE FUNCTION VALUE WITH CONSTANT: 2034.2988255371602   
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT  
   
 TOTAL EFFECTIVE ETAS (NIND\*NETA): 96  
   
 #TERE:  
 Elapsed estimation time in seconds: 1.44  
 Elapsed covariance time in seconds: 0.03  
1  
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
   
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 #OBJT:\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL VALUE OF OBJECTIVE FUNCTION \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 #OBJV:\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* 1473.746 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* FINAL PARAMETER ESTIMATE \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 -1.92E+00 9.97E-01 -7.31E-01 8.33E-01 3.24E-01 3.22E-01 1.07E-01  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 7.60E-02  
   
 ETA2  
+ 3.48E-02 2.37E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-02  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 6.79E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 2.76E-01  
   
 ETA2  
+ 8.22E-01 1.54E-01  
   
 ETA3  
+ 0.00E+00 0.00E+00 1.00E-01  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 2.61E-01  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 1.00E+00  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* STANDARD ERROR OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*\*\*\*\*  
  
  
 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7   
   
 1.12E-01 5.59E-02 1.25E-01 1.10E-01 7.67E-02 1.52E-01 6.37E-03  
   
  
  
 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 3.29E-02  
   
 ETA2  
+ 1.83E-02 1.03E-02  
   
 ETA3  
+ 0.00E+00 0.00E+00 0.00E+00  
   
 ETA4  
+ 0.00E+00 0.00E+00 0.00E+00 3.83E-02  
   
  
  
 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*  
  
  
 EPS1   
   
 EPS1  
+ 0.00E+00  
   
1  
  
  
 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*\*\*  
  
  
 ETA1 ETA2 ETA3 ETA4   
   
 ETA1  
+ 5.96E-02  
   
 ETA2  
+ 1.58E-01 3.36E-02  
   
 ETA3  
+ ......... ......... .........  
   
 ETA4  
+ ......... ......... ......... 7.34E-02  
   
  
  
 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*  
  
  
 EPS1   
   
 EPS1  
+ .........  
   
1  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.25E-02  
   
 TH 2  
+ 4.49E-03 3.12E-03  
   
 TH 3  
+ 2.14E-03 -1.32E-03 1.56E-02  
   
 TH 4  
+ -2.79E-03 -3.48E-03 -5.77E-04 1.21E-02  
   
 TH 5  
+ -1.93E-03 -8.80E-04 1.64E-03 -2.12E-03 5.89E-03  
   
 TH 6  
+ -1.18E-02 -2.86E-03 -6.25E-03 3.18E-03 3.77E-04 2.32E-02  
   
 TH 7  
+ 2.23E-04 9.71E-05 -1.09E-04 -1.81E-04 -4.46E-05 -5.07E-04 4.06E-05  
   
 OM11  
+ -6.25E-04 -4.12E-04 1.36E-03 6.42E-05 5.31E-04 -1.30E-03 1.38E-05 1.08E-03  
   
 OM12  
+ -5.77E-04 -2.89E-04 2.20E-04 2.67E-04 2.38E-04 2.56E-06 1.69E-06 5.43E-04 3.35E-04  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.65E-04 -1.59E-04 8.09E-05 9.22E-05 1.03E-04 -9.49E-05 1.24E-05 2.45E-04 1.62E-04 0.00E+00 0.00E+00 1.07E-04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 1.17E-03 1.49E-04 -8.48E-04 1.94E-03 -1.13E-03 -1.85E-03 -8.04E-06 7.25E-05 3.32E-05 0.00E+00 0.00E+00 -1.52E-05  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.46E-03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* CORRELATION MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 1.12E-01  
   
 TH 2  
+ 7.18E-01 5.59E-02  
   
 TH 3  
+ 1.53E-01 -1.89E-01 1.25E-01  
   
 TH 4  
+ -2.27E-01 -5.67E-01 -4.20E-02 1.10E-01  
   
 TH 5  
+ -2.25E-01 -2.05E-01 1.71E-01 -2.52E-01 7.67E-02  
   
 TH 6  
+ -6.90E-01 -3.35E-01 -3.29E-01 1.90E-01 3.22E-02 1.52E-01  
   
 TH 7  
+ 3.13E-01 2.73E-01 -1.37E-01 -2.59E-01 -9.14E-02 -5.23E-01 6.37E-03  
   
 OM11  
+ -1.70E-01 -2.25E-01 3.32E-01 1.78E-02 2.11E-01 -2.61E-01 6.60E-02 3.29E-02  
   
 OM12  
+ -2.82E-01 -2.82E-01 9.61E-02 1.33E-01 1.70E-01 9.19E-04 1.45E-02 9.04E-01 1.83E-02  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ -2.29E-01 -2.75E-01 6.26E-02 8.11E-02 1.29E-01 -6.02E-02 1.88E-01 7.20E-01 8.54E-01 0.00E+00 0.00E+00 1.03E-02  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 2.73E-01 6.99E-02 -1.77E-01 4.62E-01 -3.85E-01 -3.17E-01 -3.30E-02 5.77E-02 4.73E-02 0.00E+00 0.00E+00 -3.84E-02  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 3.83E-02  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* INVERSE COVARIANCE MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 TH 1 TH 2 TH 3 TH 4 TH 5 TH 6 TH 7 OM11 OM12 OM13 OM14 OM22   
 OM23 OM24 OM33 OM34 OM44 SG11   
   
 TH 1  
+ 7.27E+02  
   
 TH 2  
+ -9.37E+02 2.08E+03  
   
 TH 3  
+ -1.71E+02 2.75E+02 1.82E+02  
   
 TH 4  
+ -1.54E+02 5.02E+02 1.73E+01 2.79E+02  
   
 TH 5  
+ 1.62E+01 1.37E+02 1.71E+01 6.42E+01 2.54E+02  
   
 TH 6  
+ 4.02E+02 -3.73E+02 -3.29E+01 -7.44E+01 6.01E+01 4.16E+02  
   
 TH 7  
+ 1.17E+03 -9.50E+02 9.14E+02 -7.30E+01 8.14E+02 2.55E+03 5.65E+04  
   
 OM11  
+ 2.37E+03 -2.03E+03 -1.04E+03 5.19E+01 1.58E+02 2.17E+03 5.84E+03 2.25E+04  
   
 OM12  
+ -3.76E+03 2.67E+03 1.69E+03 -2.91E+02 -5.97E+02 -3.90E+03 -6.90E+03 -4.14E+04 8.96E+04  
   
 OM13  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM14  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
   
 OM22  
+ 1.15E+03 3.46E+02 -4.65E+02 2.65E+02 4.58E+02 1.55E+03 -6.58E+03 1.58E+04 -4.95E+04 0.00E+00 0.00E+00 5.34E+04  
   
 OM23  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 .........  
   
 OM24  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... .........  
   
 OM33  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... .........  
   
 OM34  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
 ......... ......... ......... .........  
   
 OM44  
+ 1.27E+02 -2.97E+02 1.76E+02 -3.26E+02 1.85E+02 3.79E+02 3.75E+03 5.16E+02 -1.83E+03 0.00E+00 0.00E+00 1.59E+03  
 0.00E+00 0.00E+00 0.00E+00 0.00E+00 1.82E+03  
   
 SG11  
+ ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........  
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 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* OBJECTIVE FUNCTION EVALUATION BY IMPORTANCE SAMPLING \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* EIGENVALUES OF COR MATRIX OF ESTIMATE (S) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  
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 1 2 3 4 5 6 7 8 9 10 11  
   
 1.56E-02 7.02E-02 1.48E-01 1.97E-01 3.41E-01 6.67E-01 7.97E-01 1.26E+00 1.82E+00 2.51E+00 3.17E+00  
   
 Elapsed postprocess time in seconds: 0.23  
 Elapsed finaloutput time in seconds: 0.05  
 #CPUT: Total CPU Time in Seconds, 22.914  
Stop Time:  
Mon 11 Sep 2023 03:19:27 PM CEST