Causal Inference for Cognitive Decline Using Mixed Effects Models

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2025-06-09

Goals

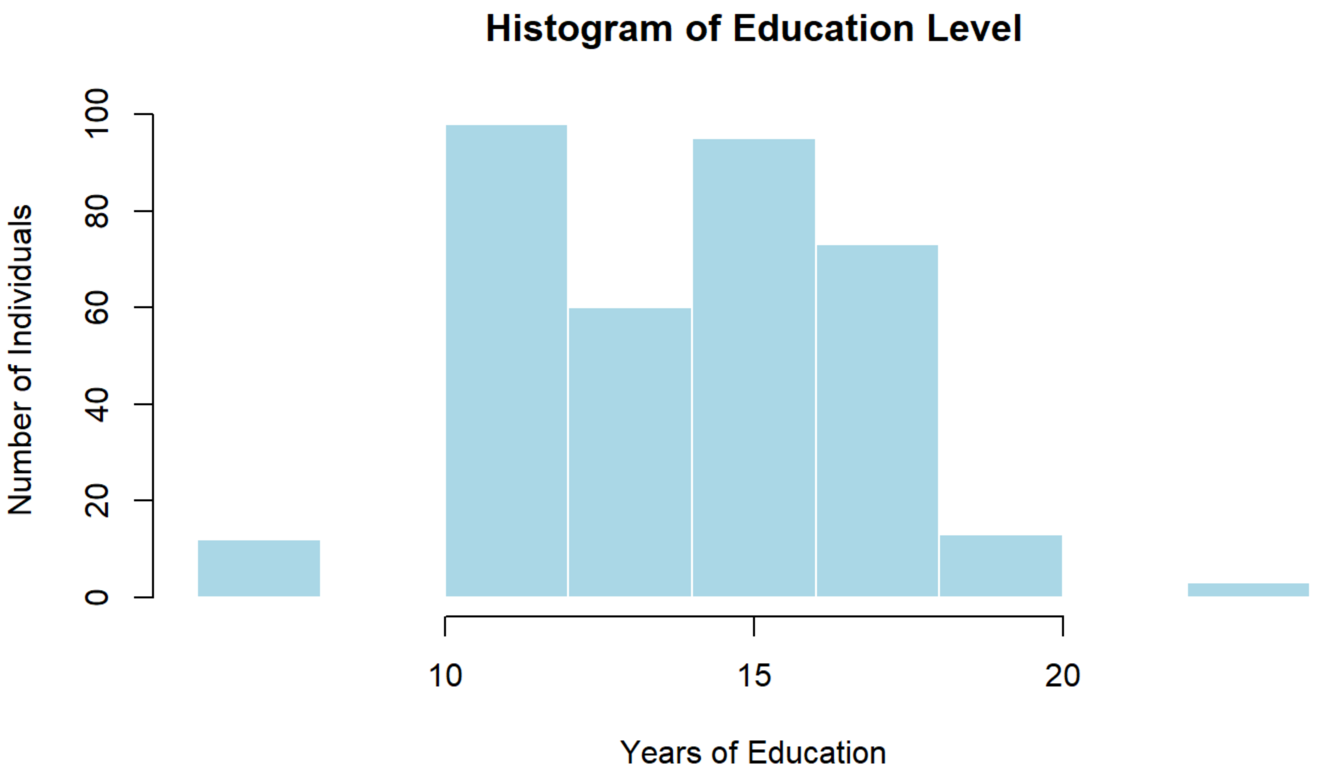
- Predictive inference for cognitive decline in Alzheimer’s disease
- Explore the limitations of LMEs on non-normal response data

Data Overview

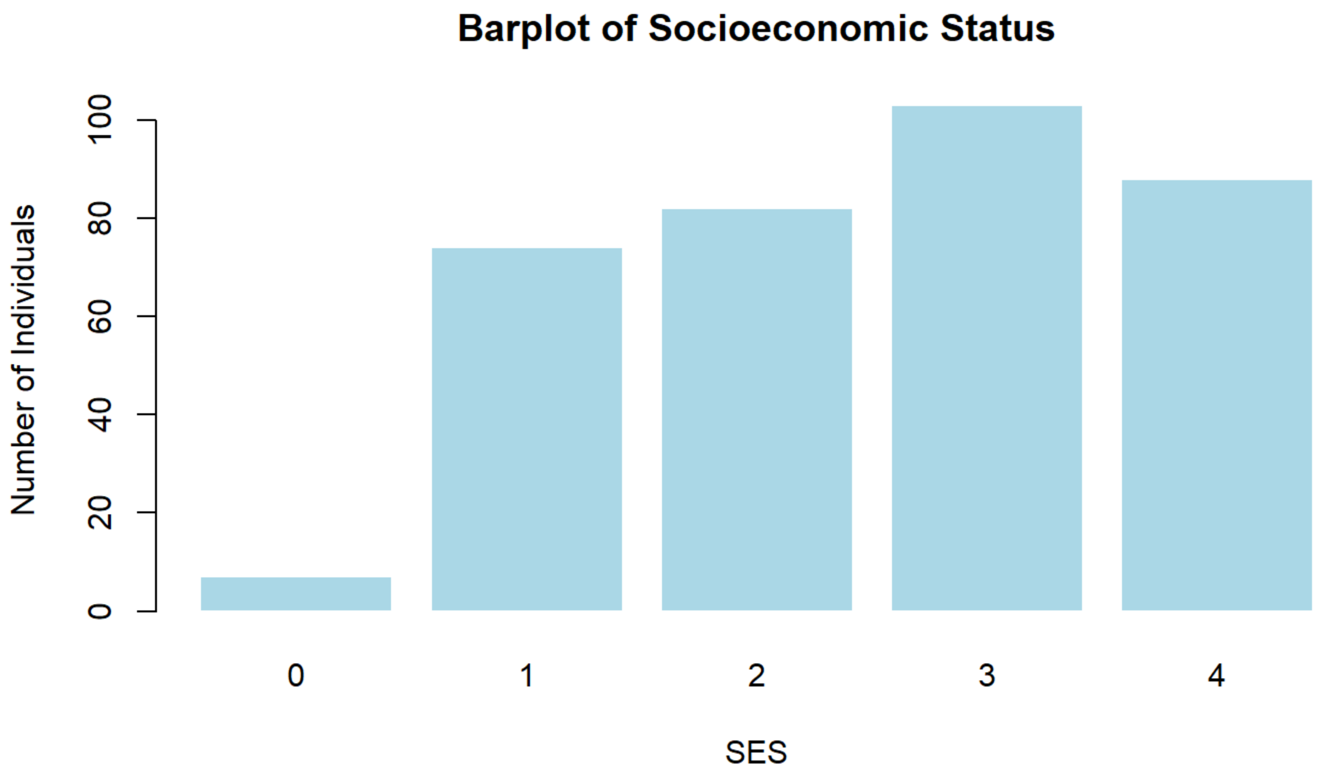
- Subject ID
- Visit number
- Sex
- Age at visit
- Years of education
- Socioeconomic status (SES): score from 0-5
- Normalized whole brain volume (nWBV): ranges from 0-1
- Mini-Mental State Examination (MMSE): test score from 0-30
- Clinical Dementia Ratio (CDR): CDR = 0 (non-demented), CDR = 0.5 (very mild Alzheimer’s), CDR = 1 (mild Alzheimer’s)

```r
df <- read.csv(
  "D:/Daniel/Documents/MATH6642/final_project/Data/oasis_longitudinal.csv")
dc <- df[!is.na(df$MMSE) & !is.na(df$SES), ]

dc$SES <- 5 - dc$SES

dc_orig <- dc

dc <- dc[order(dc$Subject.ID, dc$Age), ]
```

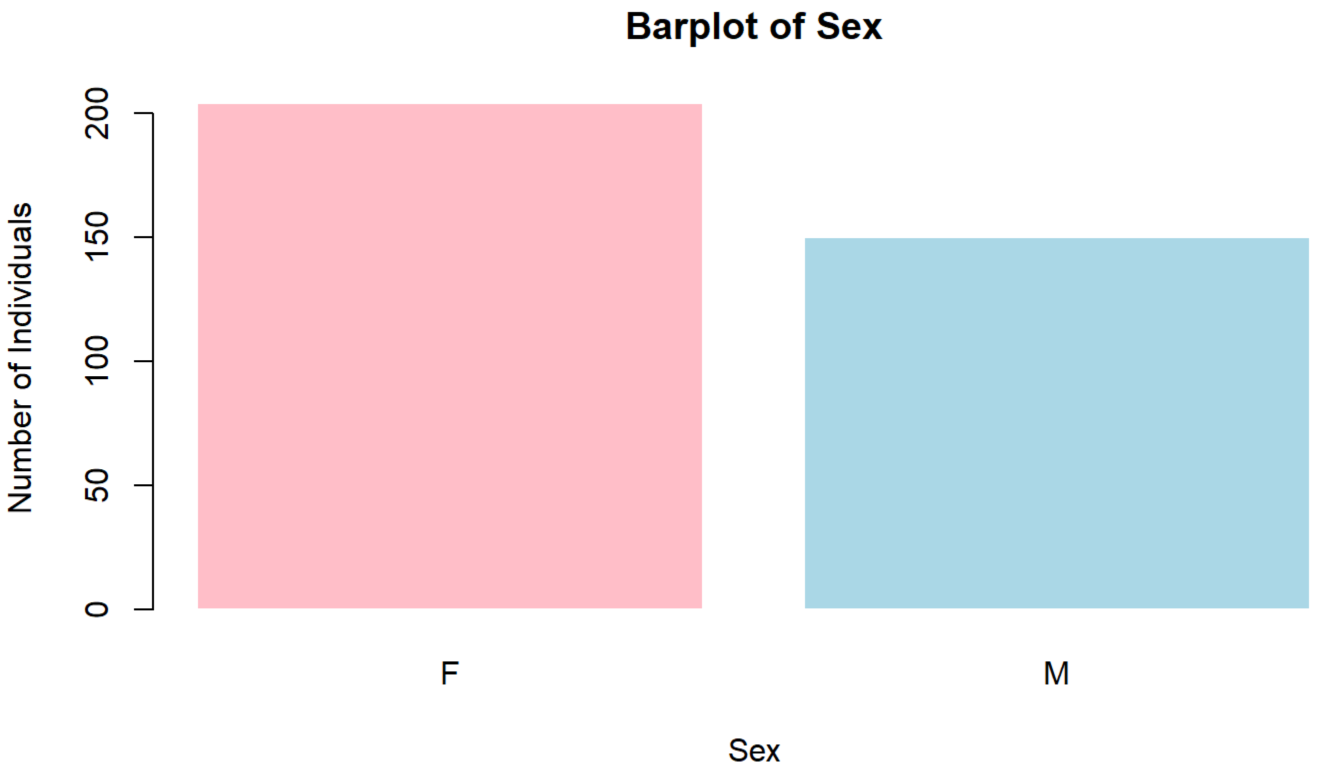
```
hist(dc$EDUC,
     breaks = 10,
     main = "Histogram of Education Level",
     xlab = "Years of Education",
     ylab = "Number of Individuals",
     col = "lightblue",
     border = "white")
```



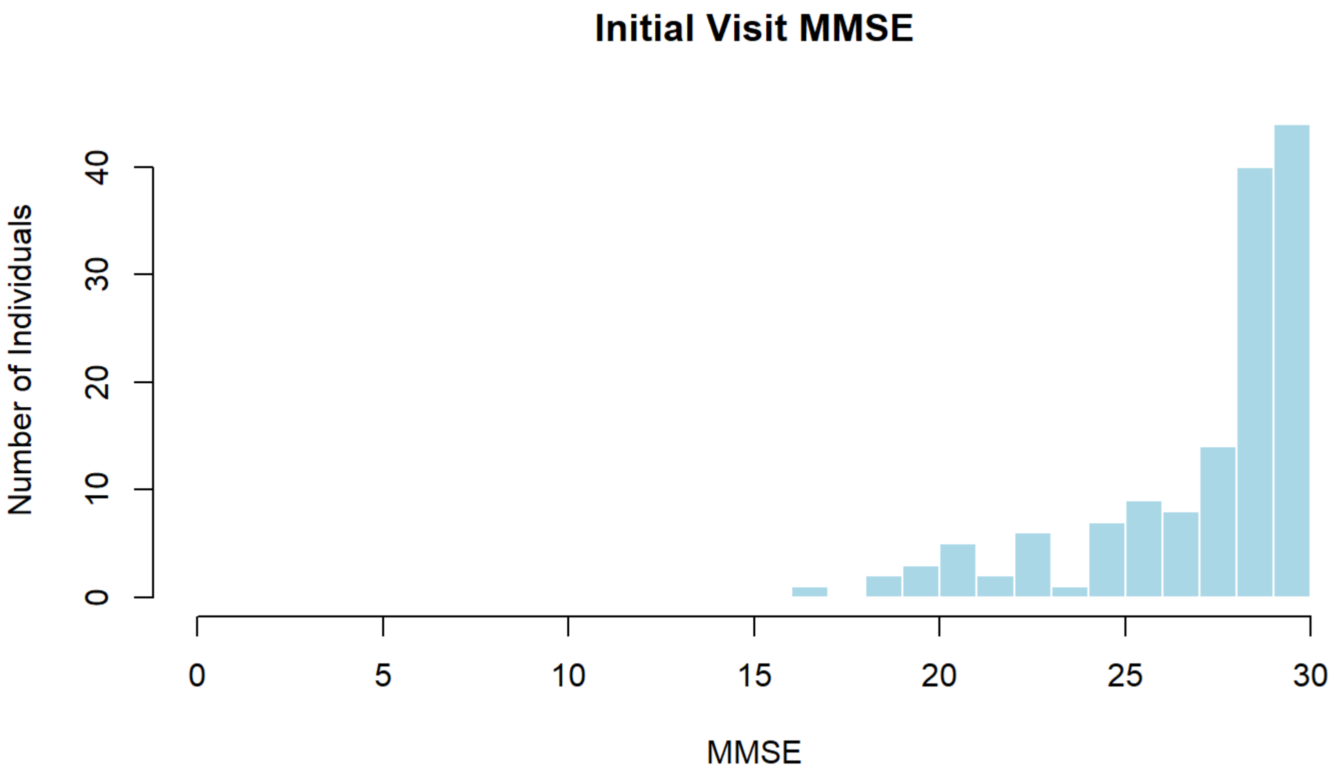
```r
barplot(table(dc$SES),
        main = "Barplot of Socioeconomic Status",
        xlab = "SES",
        ylab = "Number of Individuals",
        col = "lightblue",
        border = "white")
```



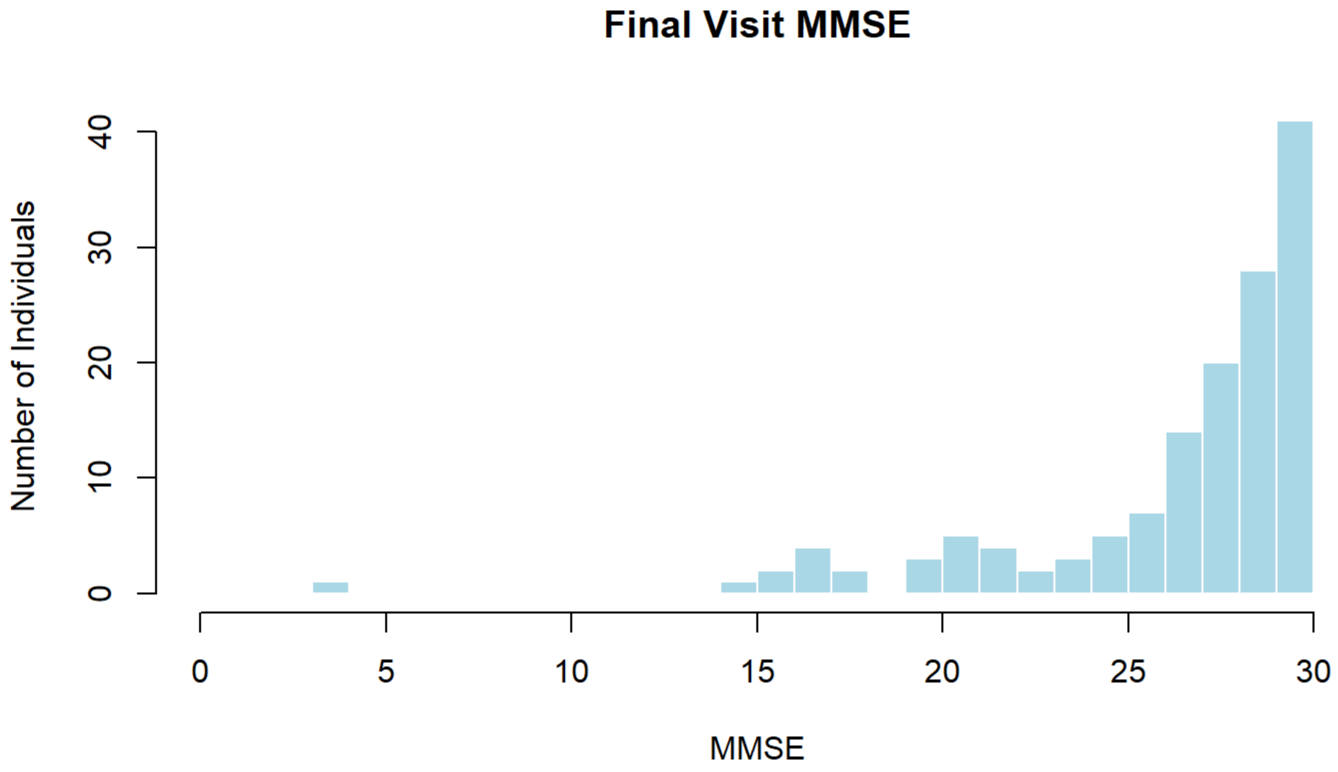
```
barplot(table(dc$M.F),
        main = "Barplot of Sex",
        xlab = "Sex",
        ylab = "Number of Individuals",
        col = c("pink", "lightblue"),
        border = "white")
```



```r
initial_visits <- dc[ave(dc$Visit, dc$Subject.ID, FUN = min) == dc$Visit, ]
final_visits <- dc[ave(dc$Visit, dc$Subject.ID, FUN = max) == dc$Visit, ]

#Histogram for initial visits
hist(initial_visits$MMSE, main = "Initial Visit MMSE", breaks = 0:30, xlab = "MMSE",
     ylab = "Number of Individuals", col = "lightblue", border = "white", xlim = c(0, 30))
```



```r
#Histogram for final visits
hist(final_visits$MMSE, main = "Final Visit MMSE", breaks = 0:30, xlab = "MMSE",
     ylab = "Number of Individuals", col = "lightblue", border = "white", xlim = c(0, 30))
```



Constructing the LME Model

Starting fixed effects:

- Age
- Years of education (EDUC)
- Socioeconomic status (SES)
- Brain volume (nWBV)
- Sex (M.F)

```r
fit1 <- lme(MMSE ~ nWBV + Age + M.F + SES + EDUC,
                  data = dc,
                  random = ~ 1 + Age | Subject.ID,
                  correlation = corAR1(form = ~ 1 | Subject.ID))
```

Random effects possibilities:

- random = ~ 1 | Subject.ID
- random = ~ 1 + Age | Subject.ID
- random = ~ 1 + nWBV

random = ~ 1 + nWBV has best AIC performance

```
fit2 <- lme(MMSE ~ nWBV + Age + M.F + SES + EDUC,
            data = dc,
            random = ~ 1 + nWBV | Subject.ID,
            correlation = corAR1(form = ~ 1 | Subject.ID),
            control = lmeControl(opt = "optim", maxIter = 200,
            msMaxIter = 200))
```

```
VarCorr(fit2)
```

```
## Subject.ID = pdLogChol(1 + nWBV)
##             Variance    StdDev    Corr
## (Intercept)  907.551971 30.125603 (Intr)
## nWBV        1463.567746 38.256604 -1
## Residual       3.542018  1.882025
```

```
summary(fit2)$tTable
```

```
##                    Value  Std.Error  DF     t-value      p-value
## (Intercept)  0.29410337 7.15721747 210  0.04109186 9.672617e-01
## nWBV        29.82370524 7.11650373 210  4.19078053 4.094784e-05
## Age          0.04380276 0.03198838 210  1.36933323 1.723578e-01
## M.FM        -0.66622466 0.44214812 138 -1.50679068 1.341500e-01
## SES          0.09387467 0.26284222 138  0.35715216 7.215235e-01
## EDUC         0.13831876 0.10419206 138  1.32753641 1.865232e-01
```

For fixed effects:

Possible 3-way interactions:

- nWBV * Age * SES: SES influences access to healthcare, slowing decay in nWBV as the subject ages.
- nWBV * Age * M.F: Possible differences in nWBV decay by sex as the subject ages.
- nWBV * Age * EDUC: Higher education slows the loss of brain volume as the subject ages.

```r
fit3 <- lme(MMSE ~ nWBV + Age + M.F + SES + EDUC + nWBV * Age * SES
            + nWBV * Age + nWBV * SES + Age * SES,
            data = dc,
            random = ~ 1 + nWBV | Subject.ID,
            correlation = corAR1(form = ~ 1 | Subject.ID),
            control = lmeControl(opt = "optim", maxIter = 200,
                                 msMaxIter = 200))
```

```
VarCorr(fit3)
```

```
## Subject.ID = pdLogChol(1 + nWBV)
##             Variance    StdDev    Corr
## (Intercept)  0.03821886 0.1954965 (Intr)
## nWBV         0.04110123 0.2027344 -0.371
## Residual    10.72286737 3.2745790
```

```
summary(fit3)$tTable
```

```
##                     Value   Std.Error  DF    t-value   p-value
## (Intercept)  -109.6451897  93.3145687 206 -1.1750061 0.2413486
## nWBV          159.7594967 127.1639879 206  1.2563266 0.2104204
## Age             1.0239979   1.2219271 206  0.8380188 0.4029914
## M.FM           -0.5032879   0.5390608 138 -0.9336385 0.3521211
## SES            29.7143769  32.3897030 138  0.9174020 0.3605326
## EDUC            0.2038590   0.1294284 138  1.5750715 0.1175297
## nWBV:Age       -1.1008893   1.6808296 206 -0.6549678 0.5132191
## nWBV:SES      -36.1186355  44.4375366 206 -0.8127956 0.4172736
## Age:SES        -0.2651406   0.4224883 206 -0.6275692 0.5309812
## nWBV:Age:SES    0.3072175   0.5846036 206  0.5255143 0.5997909
```

Let’s consider 2-way interactions instead:

- nWBV * Age : Brain volume changes with age.
- nWBV * EDUC: Education acts as a buffer against brain volume loss.
- nWBV * SES : Higher SES allows for better healthcare, improving preservation of brain volume.
- nWBV * M.F : Sex affects brain volume.
- Age * EDUC : Education acts as a buffer against age effects.
- Age * M.F : Aging affects women and men differently.
- Age * SES : Higher SES acts as a buffer against age effects by again allowing for better healthcare.

```
fit5 <- lme(MMSE ~ nWBV + Age + SES + nWBV * SES + Age * SES,
            data = dc,
            random = ~ 1 + nWBV | Subject.ID,
            correlation = corAR1(form = ~ 1 | Subject.ID),
            control = lmeControl(opt = "optim", maxIter = 200,
            msMaxIter = 200))
```

Lowest AIC so far, all terms statistically significant

```
summary(fit5)$tTable
```

```
##                    Value   Std.Error  DF   t-value      p-value
## (Intercept) -54.94655627 16.87724929 208 -3.255658 1.320700e-03
## nWBV         85.06516352 16.96378182 208  5.014516 1.136780e-06
## Age           0.24594073  0.07957674 208  3.090611 2.270739e-03
## SES          21.81791319  6.12511634 140  3.562041 5.034821e-04
## nWBV:SES    -21.04512536  6.23253893 208 -3.376654 8.755957e-04
## Age:SES      -0.07694855  0.02853928 208 -2.696233 7.587196e-03
```

```
VarCorr(fit5)
```

```
## Subject.ID = pdLogChol(1 + nWBV)
##             Variance    StdDev    Corr
## (Intercept) 1025.335434 32.020859 (Intr)
## nWBV        1677.873565 40.961855 -1
## Residual       3.402637  1.844624
```

Diagnostics for G-Matrix

Try within-subject centering?

```
test <- lme(MMSE ~ nWBV + Age + SES + nWBV * SES + Age * SES,
            data = dc,
            random = ~ 1 + dvar(nWBV, Subject.ID) | Subject.ID,
            correlation = corAR1(form = ~ 1 | Subject.ID),
            control = lmeControl(opt = "optim", maxIter = 200,
                                 msMaxIter = 200))

anova(fit5, test)
```

```
##      Model df      AIC      BIC    logLik
## fit5     1 11 1621.422 1663.796 -799.7112
## test     2 11 1643.240 1685.614 -810.6199
```

```
VarCorr(test)
```

```
## Subject.ID = pdLogChol(1 + dvar(nWBV, Subject.ID))
##                         Variance    StdDev    Corr  
## (Intercept)                7.461877  2.731644 (Intr)
## dvar(nWBV, Subject.ID) 6328.600137 79.552499 -0.733
## Residual                   2.333263  1.527502
```

```
summary(test)$tTable
```

```
##                    Value   Std.Error  DF   t-value      p-value
## (Intercept) -50.99934937 16.98716373 208 -3.002229 3.008278e-03
## nWBV         79.97829545 17.19428944 208  4.651445 5.857928e-06
## Age           0.24054110  0.08325873 208  2.889080 4.272828e-03
## SES          16.51464807  6.21054872 140  2.659129 8.747329e-03
## nWBV:SES    -15.89944668  6.38933428 208 -2.488436 1.361561e-02
## Age:SES      -0.05631244  0.02943908 208 -1.912847 5.714120e-02
```

Trade-off:

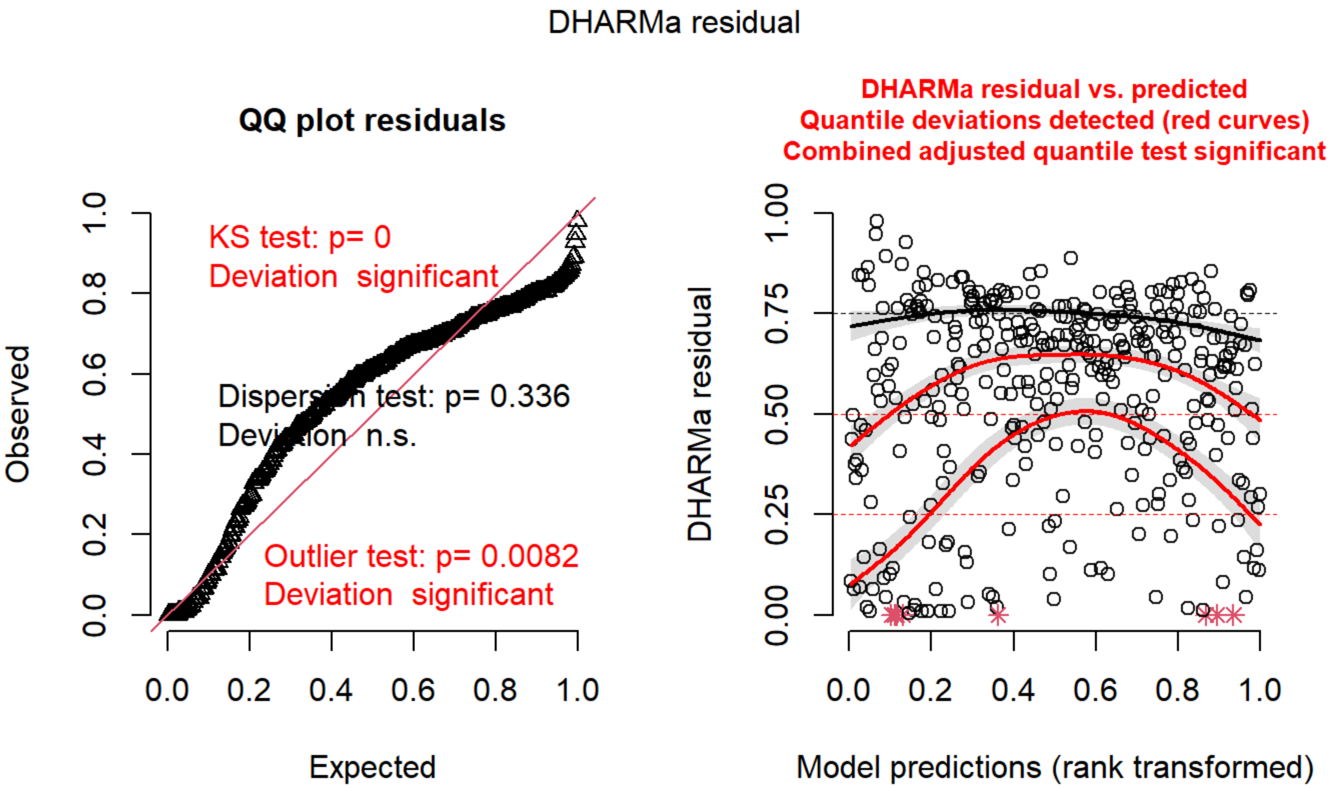
Higher AIC, loss of interaction term in exchange for stable G-matrix

Residuals

Reconstruct fit5 as a glmmTMB so we can use DHARMa to plot residuals:

```r
fit5_tmb <- glmmTMB(
  MMSE ~ nWBV + Age + SES + nWBV:SES + Age:SES + (1 + nWBV | Subject.ID),
  data = dc,
  REML = TRUE
)

res <- simulateResiduals(fittedModel = fit5_tmb)
```

```
plot(res)
```


DHARMa residual
QQ plot residuals
KS test: p= 0
Deviation significant
Dispersion test: p= 0.336
Deviation n.s.
Outlier test: p= 0.0082
Deviation significant
Observed
Expected
0.0
0.2
0.4
0.6
0.8
1.0
DHARMa residual vs. predicted
Quantile deviations detected (red curves)
Combined adjusted quantile test significant
DHARMa residual
Model predictions (rank transformed)
0.00
0.25
0.50
0.75
1.00

Problems:

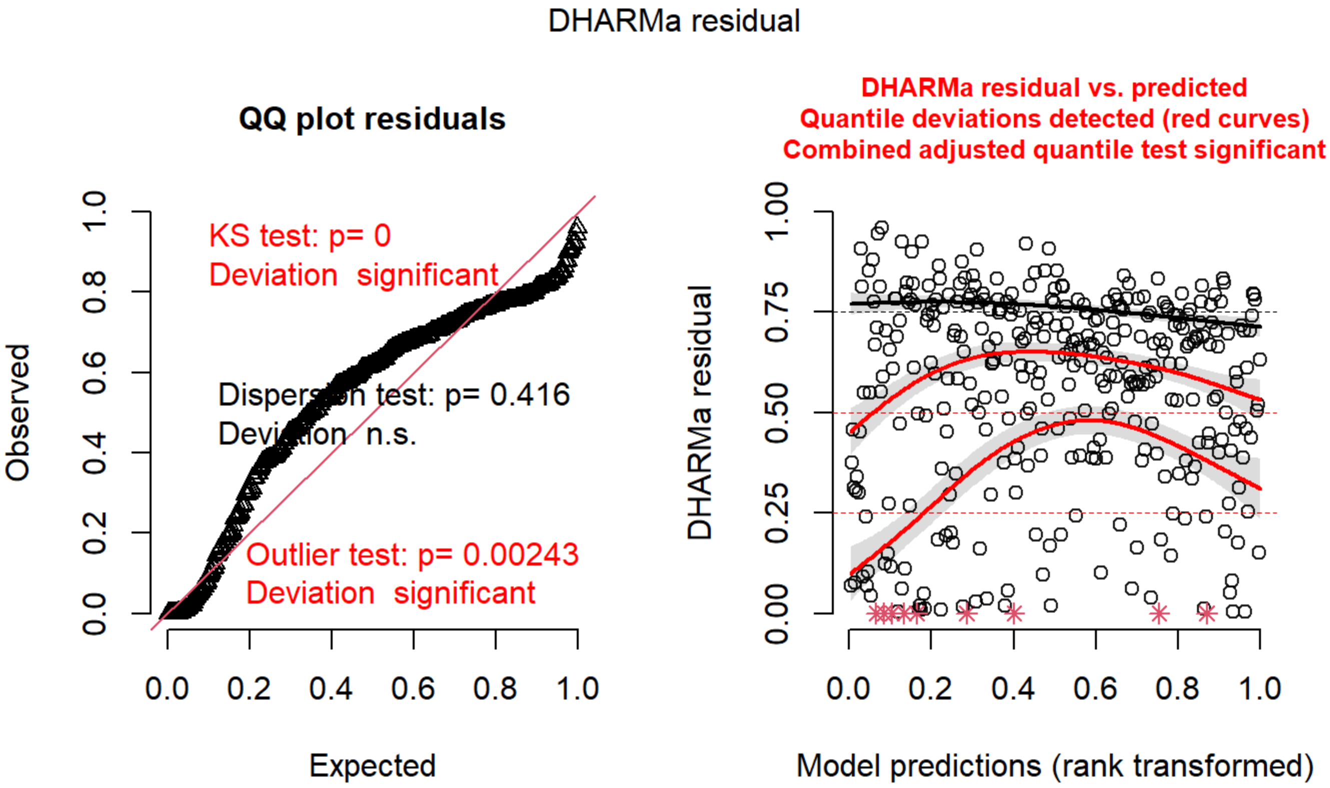
- Heteroskedasticity
- KS test: residuals are not uniformly distributed
- Outlier test: model handles outliers poorly

Let’s try non-linear terms.

```r
dc$nWBV_sq <- dc$nWBV^2

fit_nwbv_poly_raw <- glmmTMB(
  MMSE ~ nWBV + nWBV_sq + Age + SES + nWBV:SES + nWBV_sq:SES + Age:SES
  + (1 + nWBV | Subject.ID),
  data = dc,
  REML = TRUE
)

sim_nwbv_poly <- simulateResiduals(fit_nwbv_poly_raw)
```

```
plot(sim_nwbv_poly)
```

```
## Warning in newton(lsp = lsp, X = G$X, y = G$y, Eb = G$Eb, UrS = G$UrS, L = G$L,
## : Fitting terminated with step failure - check results carefully
```



```
AIC(fit_nwbv_poly_raw, fit5_tmb)
```

```
##                   df      AIC
## fit_nwbv_poly_raw 12 1601.715
## fit5_tmb          10 1628.256
```

```
dc$nWBV_scaled <- scale(dc$nWBV)[,1]
dc$nWBV_sq_scaled <- dc$nWBV_scaled^2

fit6 <- lmer(MMSE ~ nWBV_scaled + nWBV_sq_scaled + Age + SES +
             nWBV_scaled * SES + Age * SES +
             (1 + nWBV_scaled | Subject.ID),
             data = dc)
```

```
VarCorr(fit6)
```

```
##  Groups     Name        Std.Dev. Corr
##  Subject.ID (Intercept) 2.3125
##             nWBV_scaled 1.6125   -0.961
##  Residual               1.6309
```

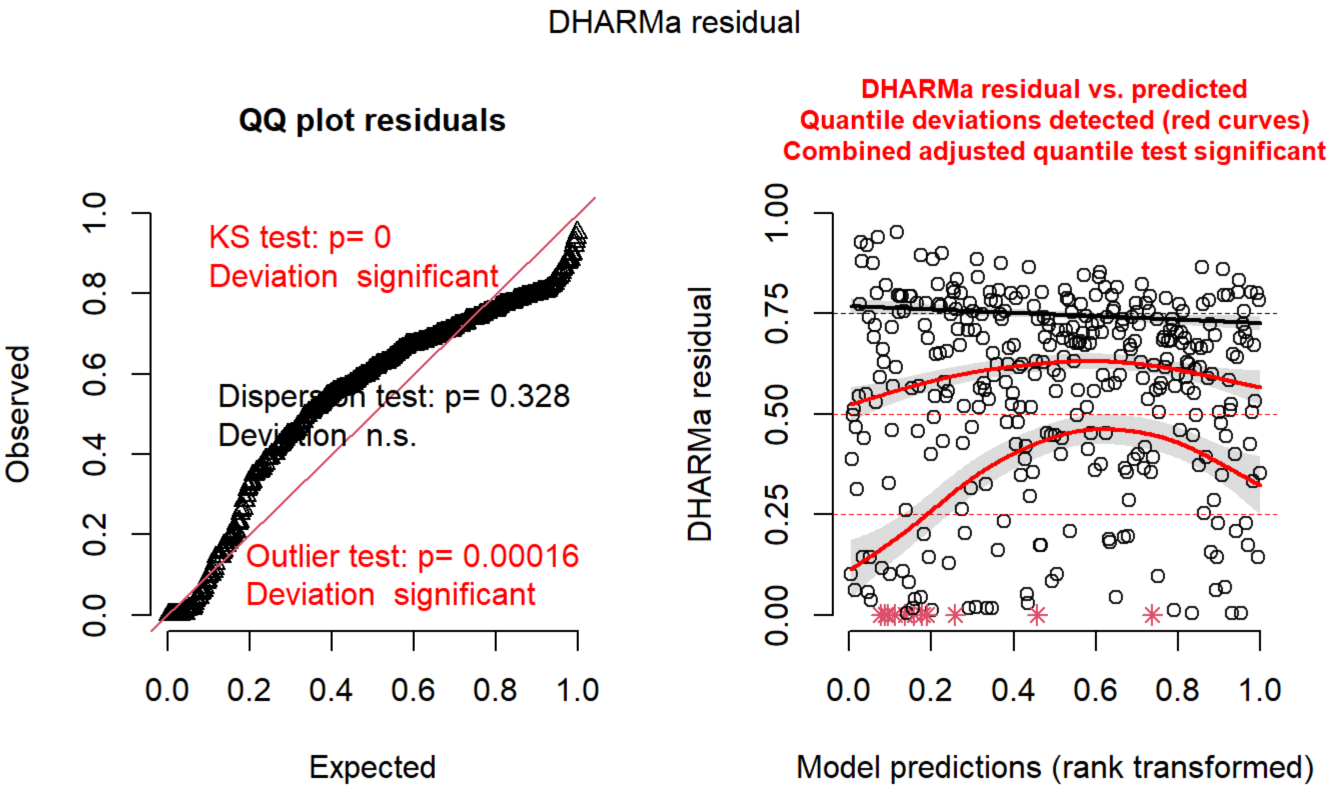
```r
as.data.frame(summary(fit6)$coefficients[, "Pr(>|t|)"])
```

```
##                  summary(fit6)$coefficients[, "Pr(>|t|)"]
## (Intercept)                                 1.878264e-01
## nWBV_scaled                                 8.595034e-08
## nWBV_sq_scaled                              2.030934e-02
## Age                                         1.861178e-03
## SES                                         1.169573e-03
## nWBV_scaled:SES                             1.926432e-04
## Age:SES                                     2.587144e-03
```

What if we try splines?

```r
dc$ns_nWBV_scaled <- ns(dc$nWBV_scaled, df = 4)
ns_basis <- ns(dc$nWBV_scaled, df = 4)
ns_df <- as.data.frame(ns_basis)
colnames(ns_df) <- paste0("ns_nWBV_", 1:ncol(ns_df))

dc <- bind_cols(dc, ns_df)

fit_spline_tmb <- glmmTMB(
  MMSE ~ ns_nWBV_1 + ns_nWBV_2 + ns_nWBV_3 + Age + SES
  + nWBV * SES + Age * SES
  + (1 + nWBV | Subject.ID),
  data = dc,
  REML = TRUE
)

res_spline <- simulateResiduals(fit_spline_tmb)
```

```
plot(res_spline)
```



```r
dc$nWBV_scaled <- scale(dc$nWBV)[,1]

fit_spline <- lmer(MMSE ~ ns(nWBV_scaled, df=4) + Age + SES +
                     nWBV_scaled*SES + Age:SES +
                   (1 + nWBV_scaled | Subject.ID),
                   data = dc,
                   REML = TRUE)
```

```
## fixed-effect model matrix is rank deficient so dropping 1 column / coefficient
```

```
VarCorr(fit_spline)
```

```
##  Groups     Name        Std.Dev. Corr
##  Subject.ID (Intercept) 2.3475
##             nWBV_scaled 1.6483   -0.953
##  Residual               1.5943
```

```r
as.data.frame(summary(fit_spline)$coefficients[, "Pr(>|t|)"])
```

```
##                           summary(fit_spline)$coefficients[, "Pr(>|t|)"]
## (Intercept)                                                 3.886609e-01
## ns(nWBV_scaled, df = 4)1                                    1.144324e-09
## ns(nWBV_scaled, df = 4)2                                    1.452616e-08
## ns(nWBV_scaled, df = 4)3                                    1.443120e-09
## ns(nWBV_scaled, df = 4)4                                    3.127850e-07
## Age                                                         1.120163e-03
## SES                                                         9.066069e-04
## SES:nWBV_scaled                                             1.472280e-04
## Age:SES                                                     1.991614e-03
```

Solution for Residuals?

Use a glmmTMB with zero-inflation.

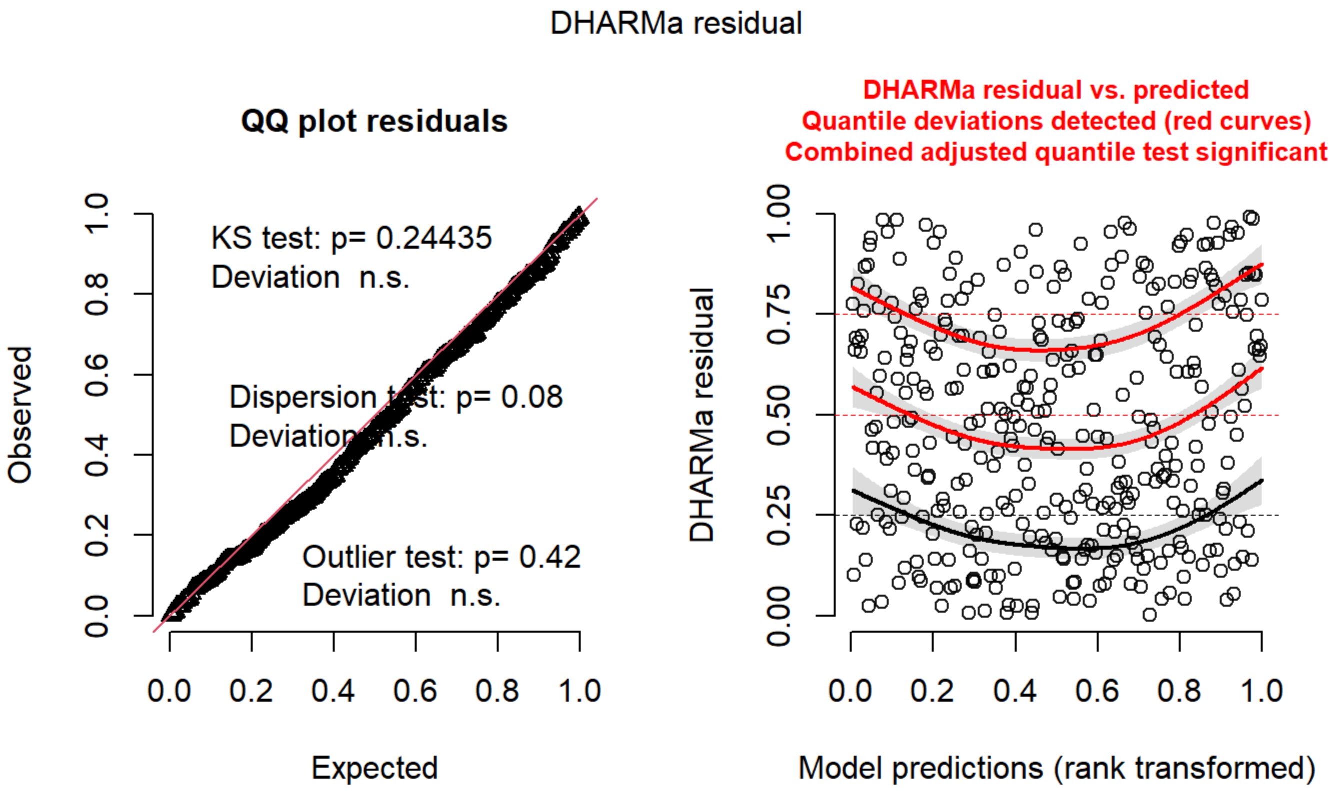
```
dc_c <- dc
dc_c$MMSE <- 30 - dc_c$MMSE
dc_c$nWBV_scaled <- scale(dc_c$nWBV)[,1]
dc_c$Age_scaled <- scale(dc_c$Age)[,1]
dc_c$SES_scaled <- scale(dc_c$SES)[,1]

fit5_tmb <- glmmTMB(
  MMSE ~ nWBV_scaled + Age_scaled + SES_scaled +
         nWBV_scaled * SES_scaled + Age_scaled * SES_scaled +
         (1 | Subject.ID),
  data = dc_c,
  ziformula = ~ Age_scaled,
  family = poisson,
  REML = TRUE
)
```

```
AIC(fit5, fit5_tmb)
```

```
## Warning in AIC.default(fit5, fit5_tmb): models are not all fitted to the same
## number of observations
```

```
##          df      AIC
## fit5     11 1621.422
## fit5_tmb  9 1305.129
```

```
res1 <- simulateResiduals(fit5_tmb)
plot(res1)
```



Model Interpretation

```
VarCorr(fit_spline)
```

```
##  Groups     Name        Std.Dev. Corr
##  Subject.ID (Intercept) 2.3475
##             nWBV_scaled 1.6483   -0.953
##  Residual               1.5943
```

```
wald(fit_spline)
```

```
##  numDF denDF F-value p-value
##      9   Inf 2915.09 <.00001
##                          Estimate  Std.Error DF  t-value   p-value Lower 0.95
## (Intercept)              -6.066963 7.019796  Inf -0.864265 0.38744 -19.825510
## ns(nWBV_scaled, df = 4)1 12.596798 1.987106  Inf  6.339268 <.00001   8.702142
## ns(nWBV_scaled, df = 4)2 12.740600 2.124430  Inf  5.997184 <.00001   8.576793
## ns(nWBV_scaled, df = 4)3 28.718316 4.562693  Inf  6.294159 <.00001  19.775602
## ns(nWBV_scaled, df = 4)4 16.685178 3.085717  Inf  5.407228 <.00001  10.637283
## Age                       0.253806 0.076411  Inf  3.321600 0.00090   0.104044
## SES                       7.112171 2.100476  Inf  3.385980 0.00071   2.995314
## SES:nWBV_scaled          -0.904538 0.231527  Inf -3.906836 0.00009  -1.358323
## Age:SES                  -0.085723 0.027222  Inf -3.149001 0.00164  -0.139077
##                          Upper 0.95
## (Intercept)               7.691585
## ns(nWBV_scaled, df = 4)1 16.491454
## ns(nWBV_scaled, df = 4)2 16.904407
## ns(nWBV_scaled, df = 4)3 37.661031
## ns(nWBV_scaled, df = 4)4 22.733073
## Age                       0.403568
## SES                      11.229029
## SES:nWBV_scaled          -0.450754
## Age:SES                  -0.032368
```

Model Comparison

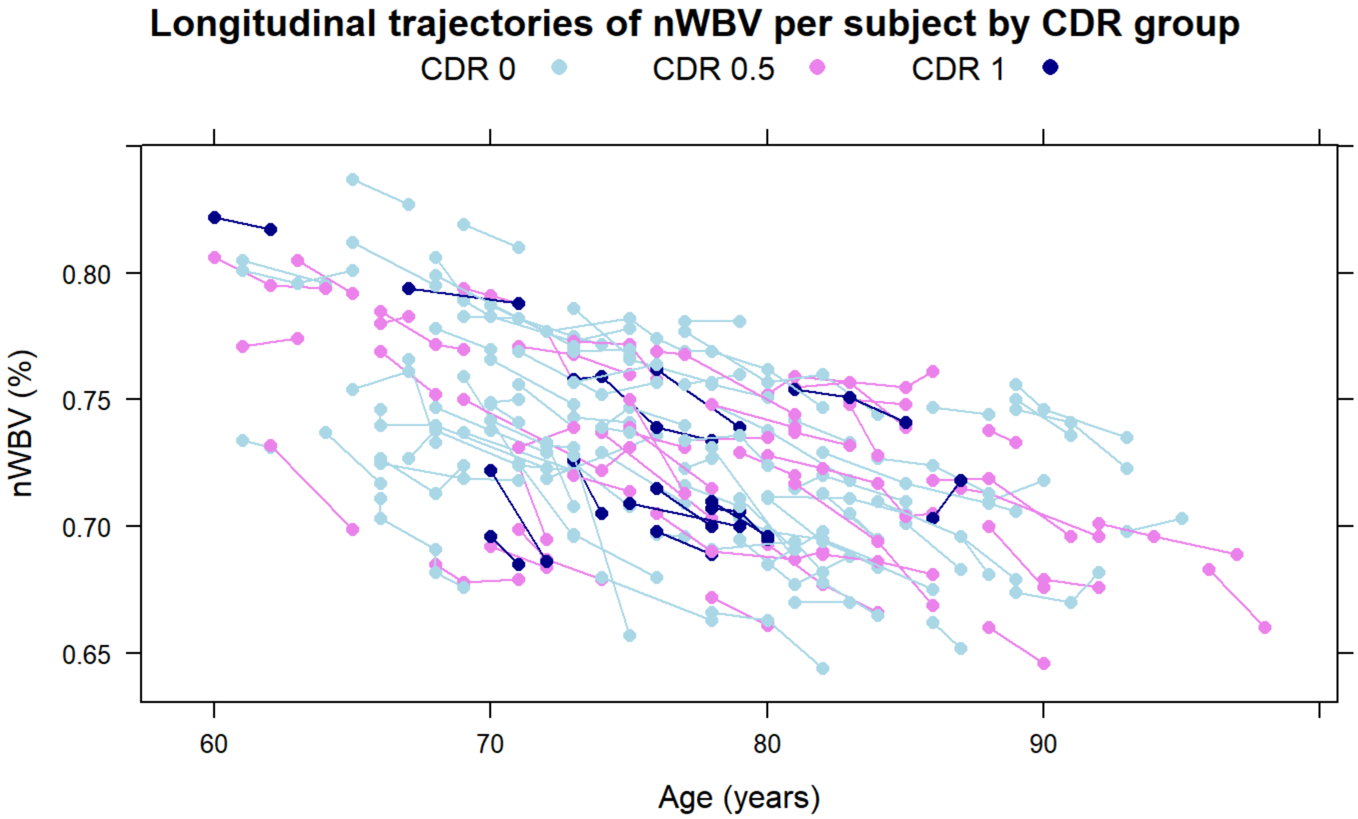
```
AIC(fit5, fit6, fit_spline)
```

```
## Warning in AIC.default(fit5, fit6, fit_spline): models are not all fitted to
## the same number of observations
```

```
##            df      AIC
## fit5       11 1621.422
## fit6       11 1639.894
## fit_spline 13 1624.226
```

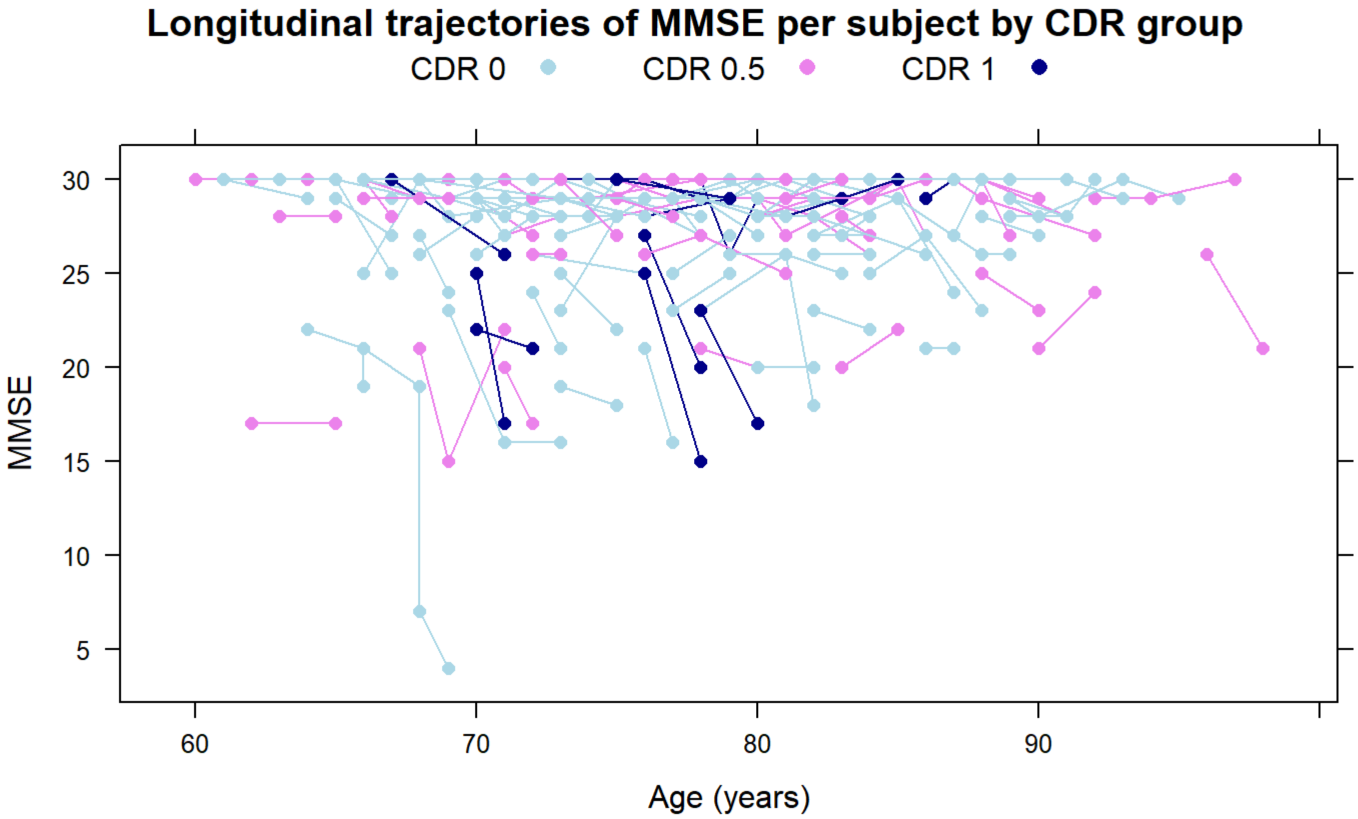
```r
cdr_colors <- c("0" = "lightblue", "0.5" = "violet", "1" = "darkblue")

#nWBV trajectories
nWBV_traj <- xyplot(nWBV ~ Age, data = dc,
       groups = Subject.ID,
       type = "b",
       lwd = 1,
       pch = 16,
       col = cdr_colors[as.character(dc$CDR)],
       xlab = "Age (years)",
       ylab = "nWBV (%)",
       main = "Longitudinal trajectories of nWBV per subject by CDR group",
       key = list(text = list(c("CDR 0", "CDR 0.5", "CDR 1")),
                  points = list(pch = 16, col = c("lightblue", "violet", "darkblue")),
                  columns = 3))
```

nWBV_traj


Longitudinal trajectories of nWBV per subject by CDR group
CDR 0 ●
CDR 0.5 ●
CDR 1 ●
nWBV (%)
0.80
0.75
0.70
0.65
60
70
80
90
Age (years)

```r
#MMSE trajectories
MMSE_traj <- xyplot(MMSE ~ Age, data = dc,
       groups = Subject.ID,
       type = "b",
       lwd = 1,
       pch = 16,
       col = cdr_colors[as.character(dc$CDR)],
       xlab = "Age (years)",
       ylab = "MMSE",
       main = "Longitudinal trajectories of MMSE per subject by CDR group",
       key = list(text = list(c("CDR 0", "CDR 0.5", "CDR 1")),
                  points = list(pch = 16, col = c("lightblue", "violet", "darkblue")),
                  columns = 3))
```

```
MMSE_traj
```


Longitudinal trajectories of MMSE per subject by CDR group
CDR 0 ●
CDR 0.5 ●
CDR 1 ●
MMSE
30
25
20
15
10
5
60
70
80
90
Age (years)

```r
dc_copy <- dc

subject_slopes <- dc_copy %>%
  group_by(Subject.ID, CDR) %>%
  filter(n() > 1) %>%  # need at least two points per subject
  summarise(
    slope = {
      fit <- lm(MMSE ~ Age, data = cur_data())
      coef(fit)["Age"]
    },
    .groups = "drop"
  )
```

```
## Warning: There was 1 warning in `summarise()`.
## ℹ In argument: `slope = { ... }`.
## ℹ In group 1: `Subject.ID = "OAS2_0001"` `CDR = 0`.
## Caused by warning:
## ! `cur_data()` was deprecated in dplyr 1.1.0.
## ℹ Please use `pick()` instead.
```

```r
avg_slopes_by_CDR_old <- subject_slopes %>%
  group_by(CDR) %>%
  summarise(
    avg_slope = mean(slope, na.rm = TRUE),
    n = n()
```

```r
dc$fit_vals5 <- fitted(fit5)

dc_slope <- dc %>%
  select(Subject.ID, Age, fit_vals5, CDR) %>%
  group_by(Subject.ID, CDR) %>%
  arrange(Age, .by_group = TRUE) %>%
  summarise(
    slope = if (n() >= 2) coef(lm(fit_vals5 ~ Age))[2] else NA_real_,
    .groups = "drop"
  )

avg_slopes_by_CDR_5 <- dc_slope %>%
  group_by(CDR) %>%
  summarise(
    avg_slope = mean(slope, na.rm = TRUE),
    n = n()
  )
```

```r
dc$fit_vals6 <- fitted(fit6)

dc_slope <- dc %>%
  select(Subject.ID, Age, fit_vals6, CDR) %>%
  group_by(Subject.ID, CDR) %>%
  arrange(Age, .by_group = TRUE) %>%
  summarise(
    slope = if (n() >= 2) coef(lm(fit_vals6 ~ Age))[2] else NA_real_,
    .groups = "drop"
  )

avg_slopes_by_CDR_6 <- dc_slope %>%
  group_by(CDR) %>%
  summarise(
    avg_slope = mean(slope, na.rm = TRUE),
    n = n()
  )
```

```r
dc$fit_spline <- fitted(fit_spline)

dc_slope <- dc %>%
  select(Subject.ID, Age, fit_spline, CDR) %>%
  group_by(Subject.ID, CDR) %>%
  arrange(Age, .by_group = TRUE) %>%
  summarise(
    slope = if (n() >= 2) coef(lm(fit_spline ~ Age))[2] else NA_real_,
    .groups = "drop"
  )

avg_slopes_by_CDR <- dc_slope %>%
  group_by(CDR) %>%
  summarise(
    avg_slope = mean(slope, na.rm = TRUE),
    n = n()
  )
```

```
print(avg_slopes_by_CDR_old)
```

```
## # A tibble: 3 × 3
##     CDR avg_slope     n
##   <dbl>     <dbl> <int>
## 1   0     -0.0306    76
## 2   0.5   -0.464     38
## 3   1     -0.826      9
```

```
print(avg_slopes_by_CDR_5)
```

```
## # A tibble: 4 × 3
##     CDR avg_slope     n
##   <dbl>     <dbl> <int>
## 1   0     0.00224    86
## 2   0.5  -0.160      61
## 3   1    -0.946      22
## 4   2   NaN           3
```

```
print(avg_slopes_by_CDR_6)
```

```
## # A tibble: 4 × 3
##     CDR avg_slope     n
##   <dbl>     <dbl> <int>
## 1   0     -0.0135    86
## 2   0.5   -0.227     61
## 3   1     -1.20      22
## 4   2    NaN          3
```

```
print(avg_slopes_by_CDR)
```

```
## # A tibble: 4 × 3
##     CDR avg_slope     n
##   <dbl>     <dbl> <int>
## 1   0     -0.0198    86
## 2   0.5   -0.302     61
## 3   1     -1.29      22
## 4   2    NaN          3
```

- Model with only linear terms is closest for CDR = 1
- Spline model is closest for CDR = 0, CDR = 0.5
- Incorporating non-linearity seems to steepen the mean decline for each CDR group

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Thanks for your attention!