Alternatives to MMRM for Preclinical Alzheimer's Trials

Simulated Impact of COVID-19 Hiatus on A4

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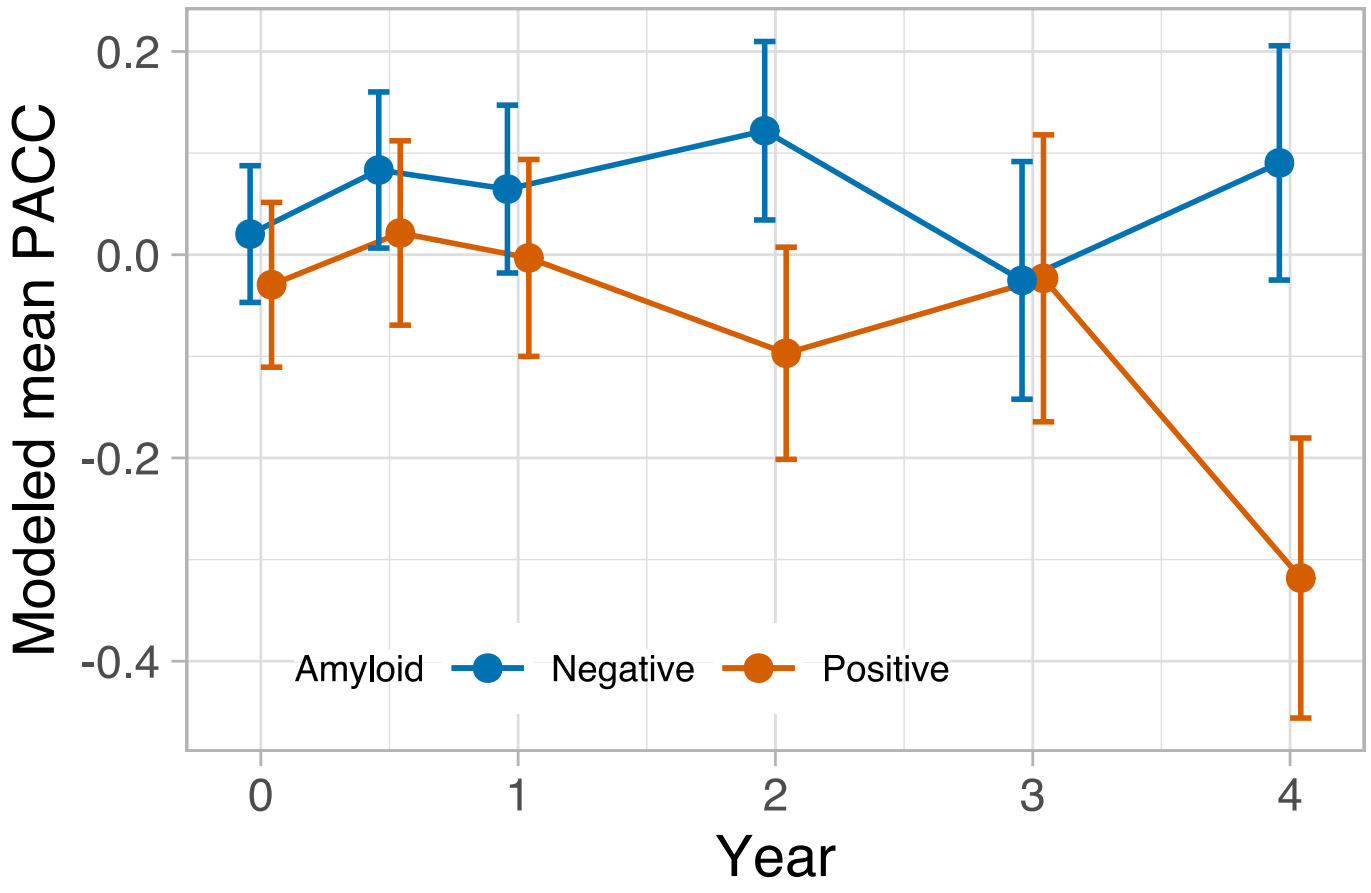
Disclosures

- M. Donohue has served on scientific advisory boards for Biogen, Eli Lilly, and Neurotrack; and has consulted for Roche. His spouse is a full-time employee of Janssen.
- This talk will discuss alternative analysis approaches for the A4 study, but no decisions have been made regarding any changes to the analysis plan. The opinions and interpretations expressed are those of M. Donohue.

Alternatives to MMRM for Preclinical AD Trials

- The Mixed Model for Repeated Measures [MMRM; Mallinckrodt, Clark, and David (2001) @] is the most commonly used approach for assessing treatment effects in Alzheimer's clinical trials.
- An alternative nonlinear Disease Progression Model (DPM) which assumes the ratio of group means is fixed over time was proposed for DIAN-TU [e.g. Wang, Berry, Xiong, Hassenstab, Quintana, McDade, Delmar, Vestrucci, Sethuraman, Bateman, and others (2018)].
- We assess alternative linear, nonlinear, and generalized additive models for Preclinical Alzheimer's clinical trials like the A4 Study (Sperling, Rentz, Johnson, Karlawish, Donohue, Salmon, and Aisen, 2014) with
    - real ADNI data and
    - simulated A4 data.
- We also simulate the impact of variable lengths of participant hiatus in treatment and follow-up in A4 due to the COVID-19 pandemic.

MMRM fit to ADNI cognitively normal amyloid pos. vs neg.



MMRM:

- Group 1 mean at t_i: β_i
- Group 2 mean at t_i: γ_i
- $i = 1, \ldots, m$ (m visits)

MMRM assumptions and fitting in R

$$Y_i = X_i\beta + \epsilon_i,$$

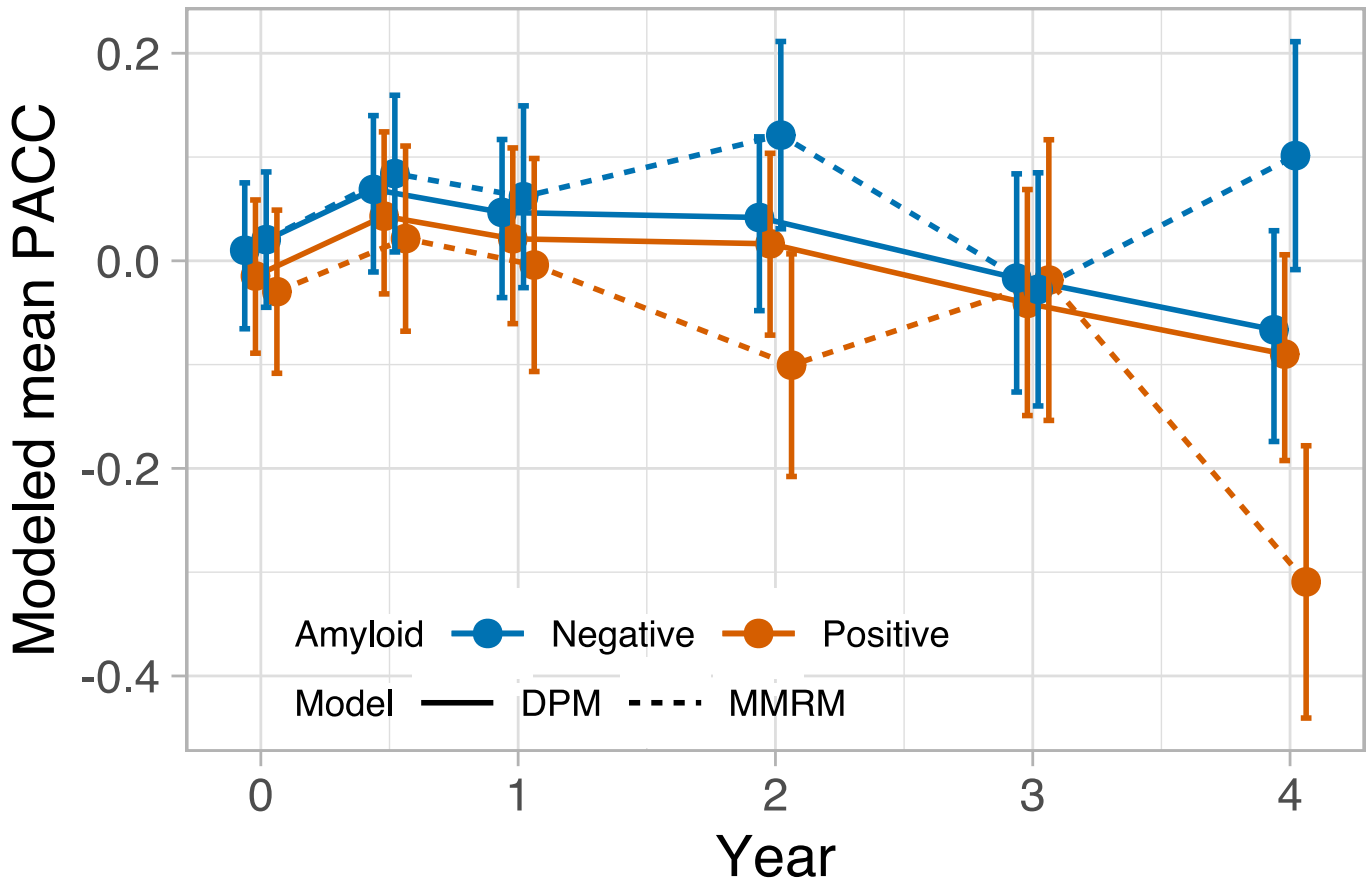
where:

- Y_i is vector of observations (one for each visit) for individual $i = 1, \ldots, n$
- X_i is matrix of fixed effect covariates for subject i
- β is vector of fixed effects to be estimated
- $\epsilon_i \sim N(0, \Sigma)$ vector of correlated residuals for subject i

Fit in `R`, using `nlme::gls`:

```
gls(pacc.ch ~ pacc.bl.c + age.c + edu.c + apoe4 + suvr.c + # bl covs
  MONTH + active:MONTH,          # mean over time (MONTH categorical)
  correlation = corSymm(form = ~ visNo | id), # general correlation
  weights = varIdent(form = ~ 1 | wk))        # heterogeneous variance
```

Disease Progression Model (DPM) fit to ADNI



DPM:

- Group 1 mean at t_i: β_i
- Group 2 mean at t_i: $\beta_i \times \theta$
- $i = 1, \ldots, m$ (m visits)
- Assumes:

$$\frac{\text{Group 1 mean at } t}{\text{Group 2 mean at } t} = \theta$$

where θ, *disease rate ratio*, is constant over time

DPM assumptions and fitting in R

$$Y_i = X_i\beta + (Z_i\gamma)(1 + \text{active}_i\theta) + W_i b_i + \epsilon_i,$$

where:

- Y_i is vector of observations (change from baseline at each visit) for individual $i = 1, \ldots, n$
- X_i, Z_i, W_i are covariates for subject i
- β is fixed effect parameter vector for baseline covariates
- γ is fixed effect parameter for placebo group temporal mean trend
- θ is *multiplicative* fixed effect parameter for relative effect of treatment
- $b_i \sim N(0, \Sigma)$ is vector of random effects

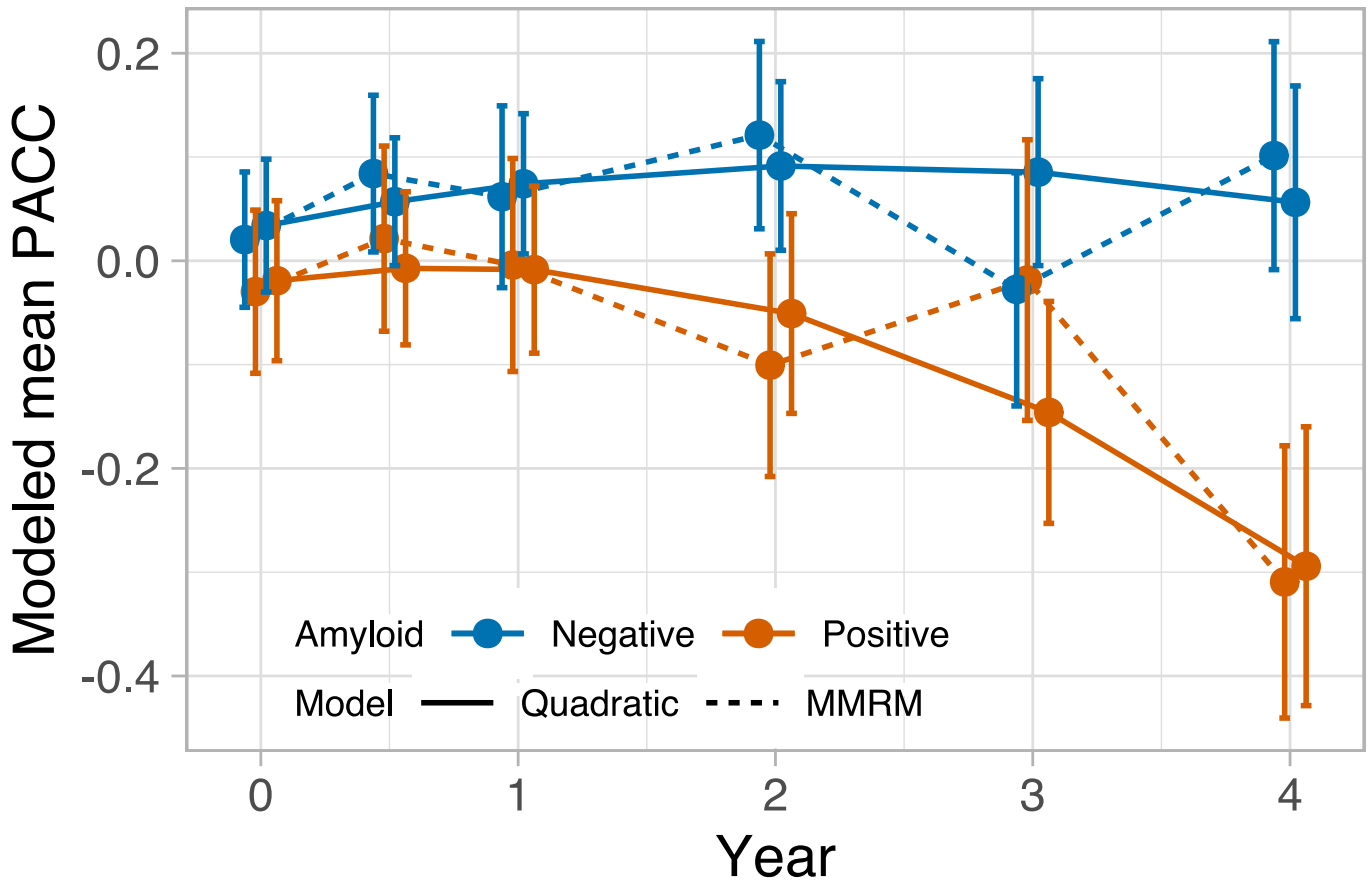
DPM assumptions and fitting in R

Fit in R, using `nlme::nlme`:

```
nlme(pacc ~ my_nonlinear_function(...), ...)

my_nonlinear_function <- function(active,
  theta,
  beta_m0, beta_m12, beta_m24, beta_m36, beta_m48,
  beta_age, beta_edu,
  M, age, edu)
{
  (I(M==0) * beta_m0 + I(M==12) * beta_m12 + I(M==24) * beta_m24 +
   I(M==36) * beta_m36 + I(M==48) * beta_m48) * (1 + theta*active) +
  age*beta_age + edu*beta_edu
}
```

Quadratic time model fit to ADNI amyloid positive vs negative



Quadratic time model:

- Group 1 mean at t: $\beta_0 + t\beta_1 + t^2\beta_2$
- Group 2 mean at t: $\gamma_0 + t\gamma_1 + t^2\gamma_2$
- $i = 1, \ldots, m$ (m visits)

Quadratic time model assumptions and fitting in R

$$Y_i = X_i\beta + \epsilon_i,$$

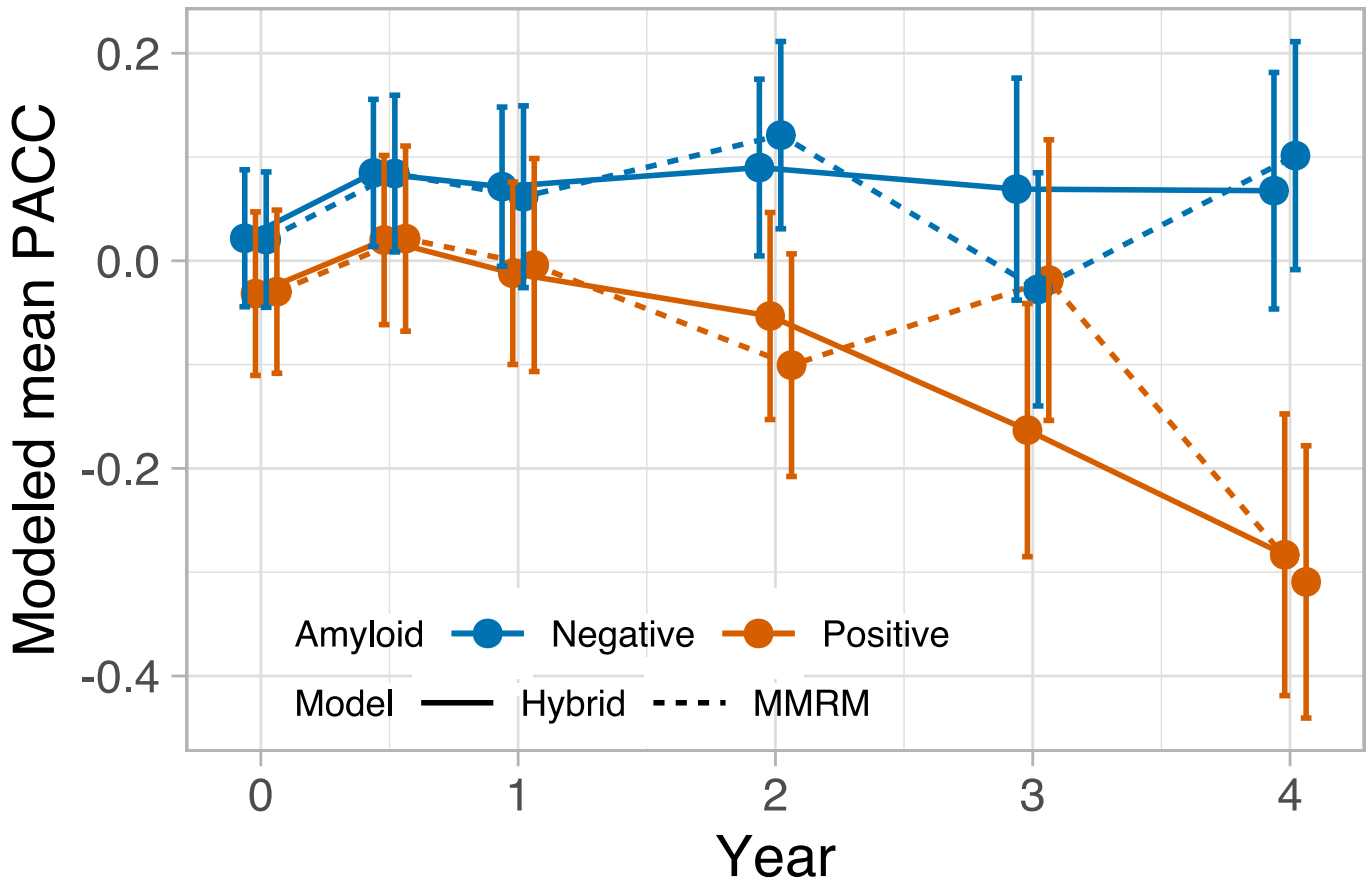
where:

- Y_i is vector of observations (one for each visit) for individual $i = 1, \ldots, n$
- X_i is matrix of fixed effect covariates for subject i
- β is vector of fixed effects to be estimated
- $\epsilon_i \sim N(0, \Sigma)$ vector of correlated residuals for subject i

Fit in `R`, using `nlme::gls`:

```
gls(pacc ~  age.c + edu.c + apoe4 + suvr.c +  # bl covs
    (months + I(months^2)) +                  # mean over time
    (months + I(months^2)):active,            # (months continuous)
  correlation = corSymm(form = ~ visNo | id), # general correlation
  weights = varIdent(form = ~ 1 | wk))        # heterogeneous variance
```

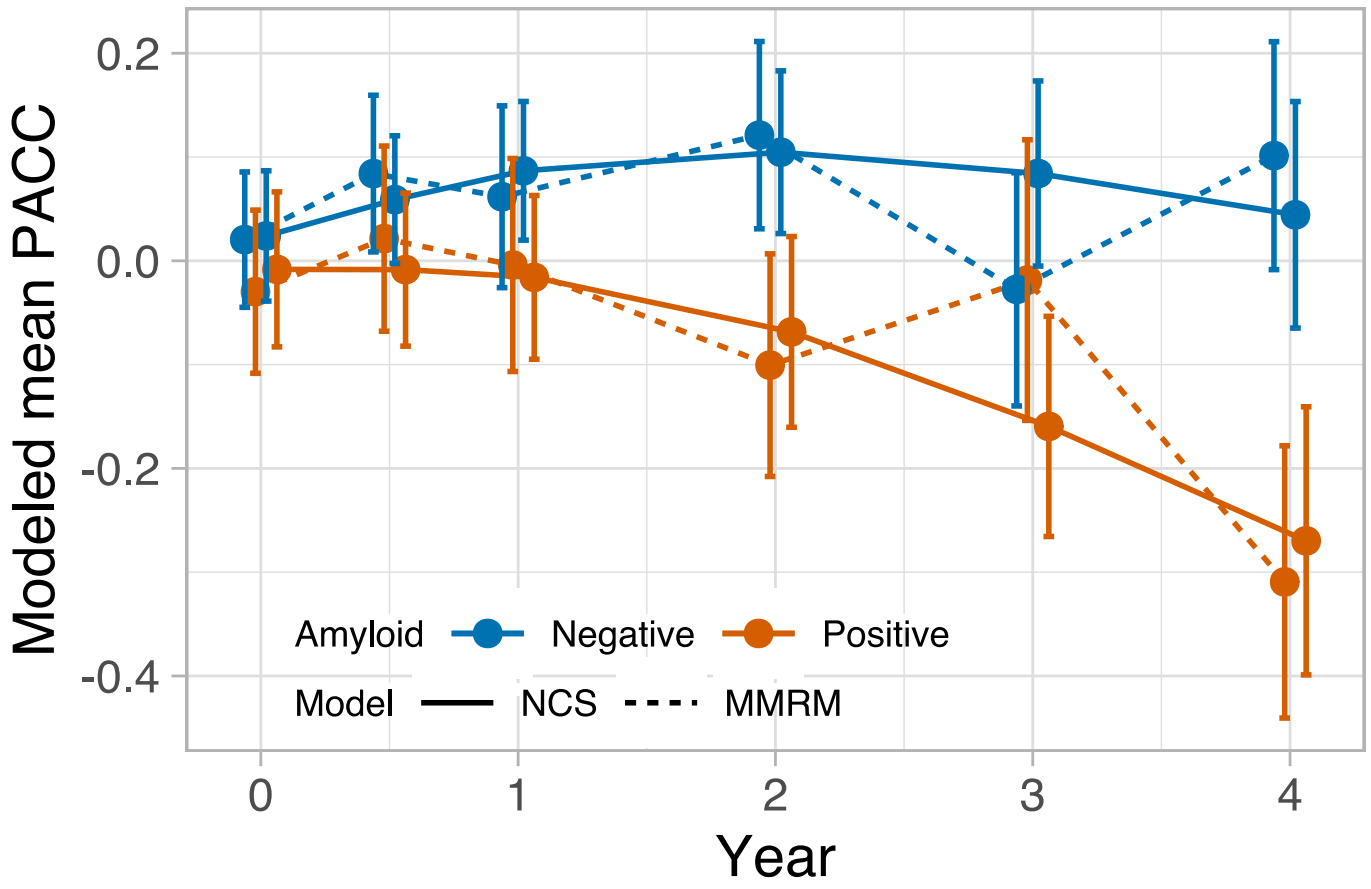
Hybrid: Categorical + Quadratic time model fit to ADNI



Hybrid model:

- Group 1 mean at t_i: β_i
- Group 2 mean at t_i: $\beta_i + \gamma_0 + t_i\gamma_1 + t_i^2\gamma_2$
- $i = 1, \ldots, m$ (m visits)

Natural Cubic Spline fit to ADNI



Natural Cubic Spline (Schoenberg, 1968):

- Group 1 mean at t: $f_1(t)$
- Group 2 mean at t: $f_2(t)$
- f_1 and f_2 are two smooth functions
  - cubic basis functions
  - natural" implies second derivatives are zero at boundaries

Natural Cubic Spline model assumptions and fitting in R

$$Y_i = X_i\beta + \epsilon_i,$$

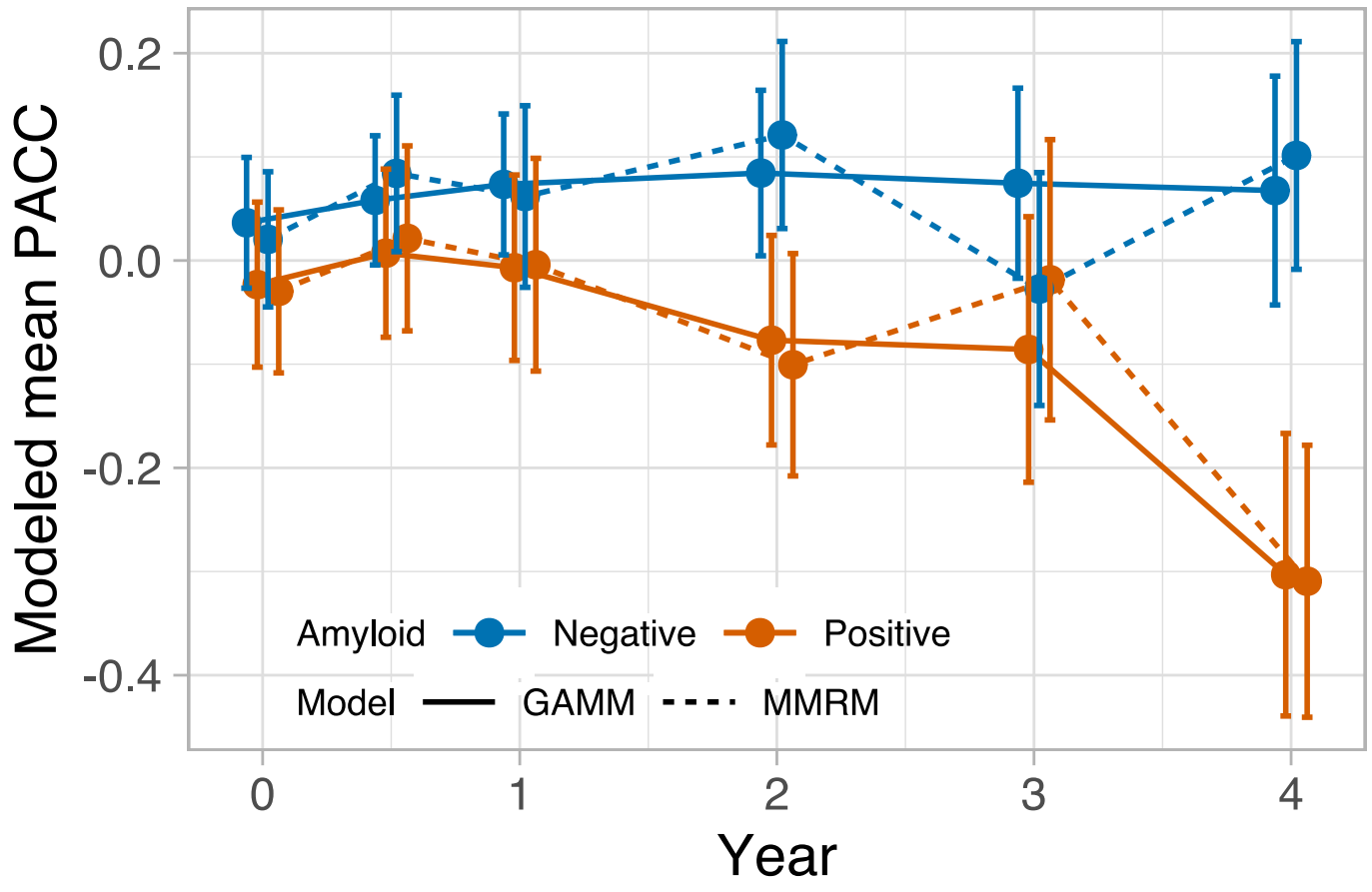
where:

- Y_i is vector of observations (one for each visit) for individual $i = 1, \ldots, n$
- X_i is matrix of fixed effect covariates for subject i
  - (including terms from the basis expansion)

Fit in `R`, using `nlme::gls`:

```
gls(pacc ~  age.c + edu.c + apoe4 + suvr.c +   # bl covs
    ns(months, df=2) +        # natural spline for placebo (1 knot)
    ns(months, df=2):active + # natural spline for active (1 knot)
  correlation = corSymm(form = ~ visNo | id), # general correlation
  weights = varIdent(form = ~ 1 | visNo))     # heterogeneous variance
```

Generalized Additive Mixed Model (GAMM) fit to ADNI



GAMM:

- Group 1 mean at t: $f_1(t)$
- Group 2 mean at t: $f_2(t)$
- f_1 and f_2 are two smooth functions
  - Thin plate regression spline
  - Smoothness penalty tuned by Generalized Cross Validation (Wood, 2017)

GAMM assumptions and fitting in R (Wood, 2017)

$$Y_i = X_i\beta + f(Z_i) + \epsilon_i,$$

where:

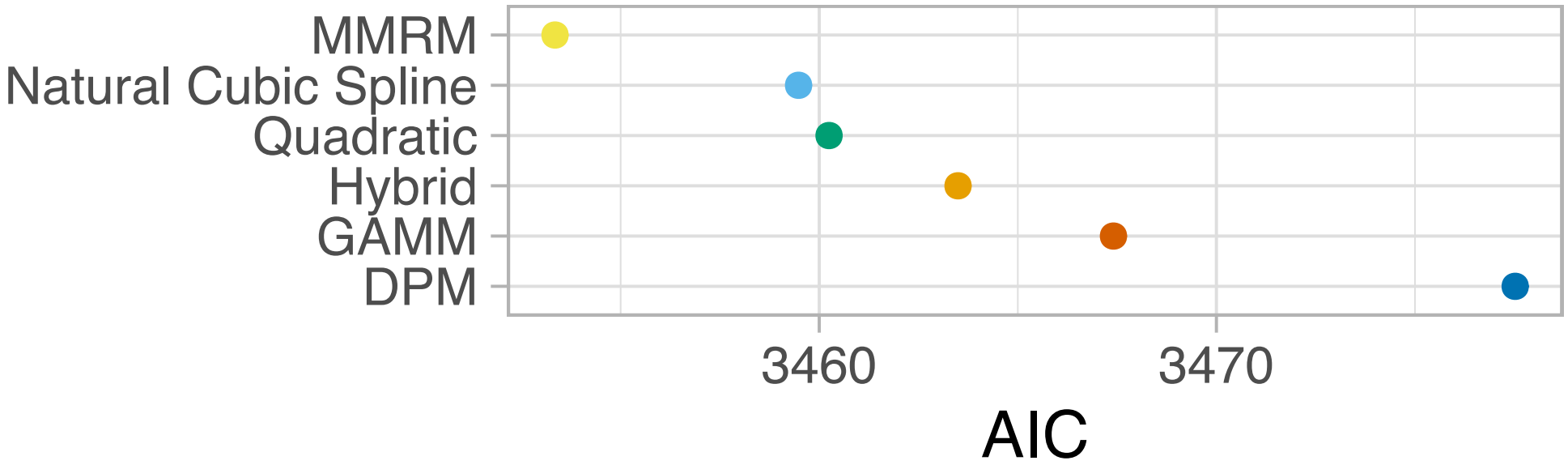
- Y_i is vector of observations (one for each visit) for individual $i = 1, \ldots, n$
- X_i, Z_i are fixed effect covariates for subject i
- f is a smooth semiparametric function to be estimated

Fit in `R`, using `mgcv::gamm`:

```
gamm(pacc ~ age.c + edu.c + apoe4 + suvr.c +  # bl covs
  s(months) + s(months, by=active, pc=0),
  correlation = corSymm(form = ~ visNo | id), # general correlation
  weights = varIdent(form = ~ 1 | visNo))     # heterogeneous variance
```

`s(months, by=active, pc=0)` provides constraint such that `f(0)=0`.

AIC for each model fit to ADNI



- All models fit with random intercept and slope
- Similar order with other correlation structures (when supported)

Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Trial: Simulated Impact of COVID-19 Hiatus

Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Trial

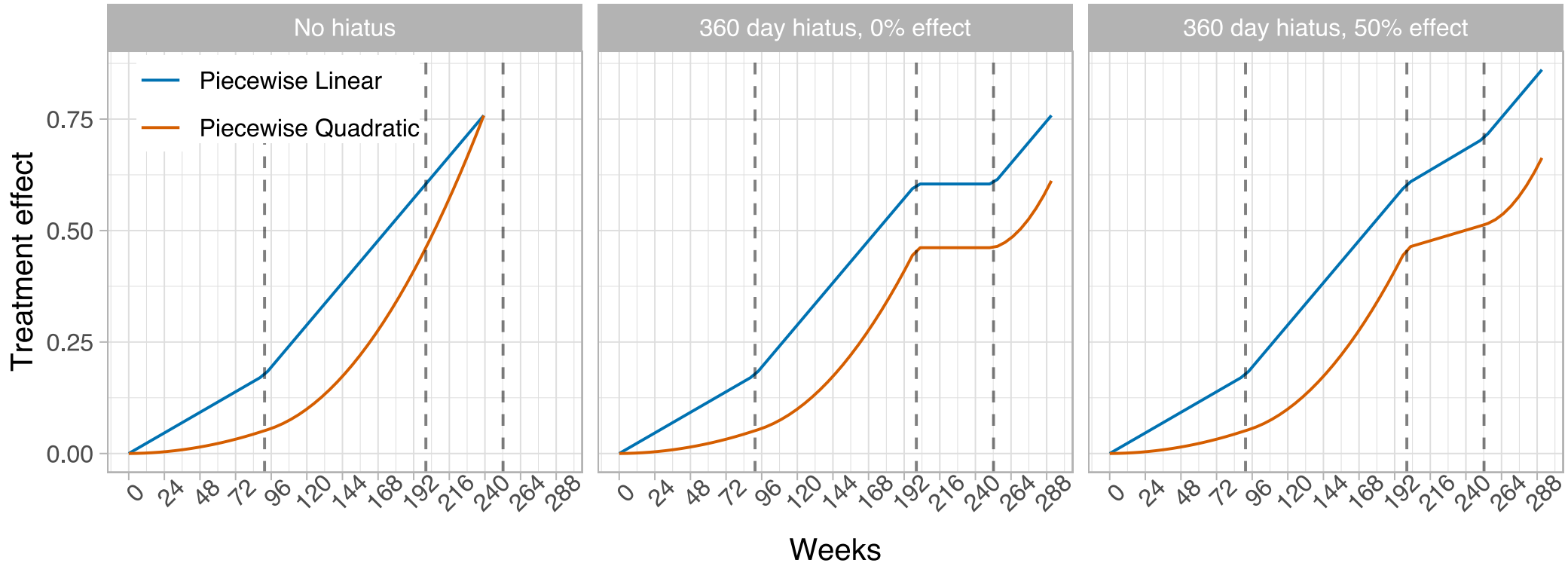
- A4 is an ongoing randomized trial in a Preclinical AD population (approx 1150 randomized).
- Double-blind period is 4.5 years; monthly infusions; biannual cognitive testing.
- In March 2020, infusions and cognitive testing were paused for most A4 participants due to COVID-19.
- Participants have been returning to their sites and will be able to receive all of the originally planned monthly doses after their "hiatus".

A4 COVID-19 Hiatus Simulations

We simulated A4 trial data under 0, 3, 6, 9, and 12 month hiatus scenarios. The simulated scenarios assume:

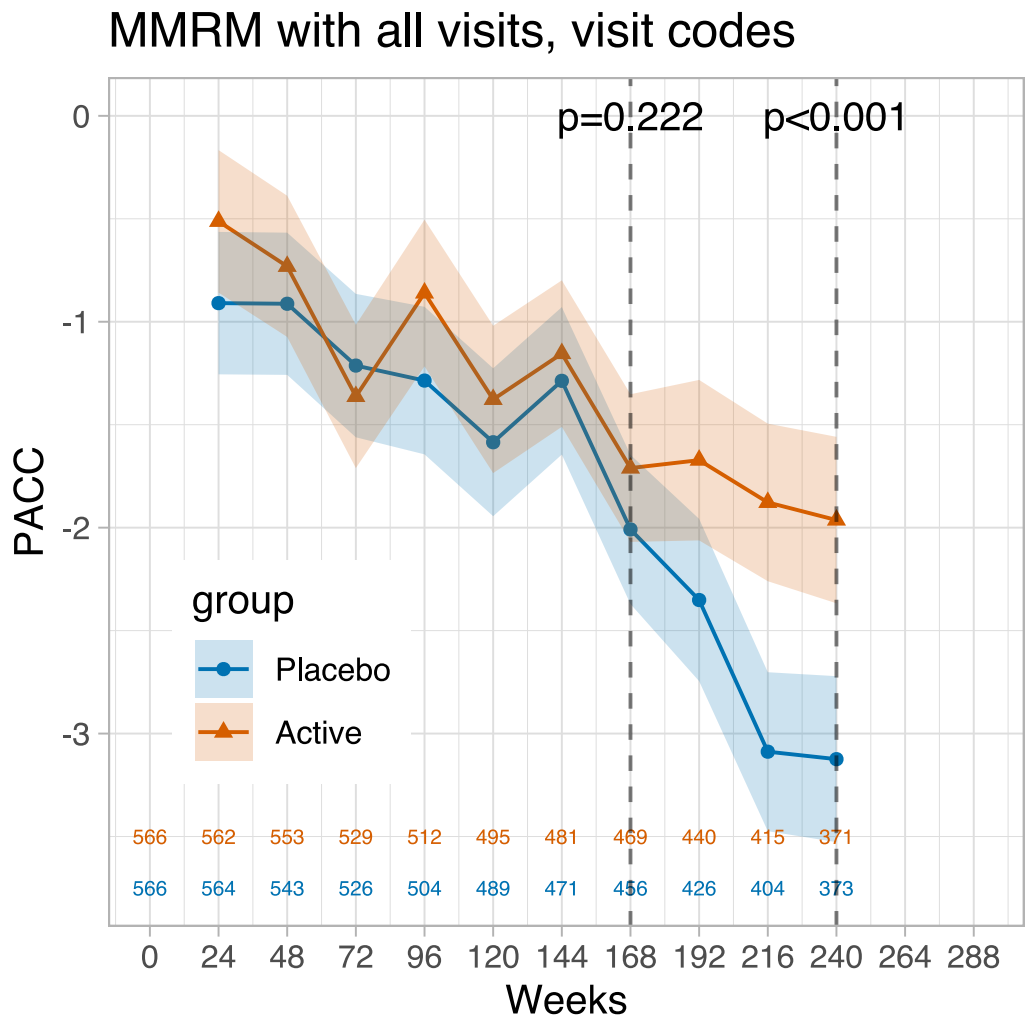
- All visits scheduled to occur after 2020-03-16 are shifted by 0, 3, 6, 9, or 12 months.
- Placebo group simulated based on models fit to data from the Harvard Aging Brain Study (HABS).
  - Fixed effects included age, APOE, amyloid PET SUVR, PACC version
- Treatment group trajectories are simulated with a piecewise linear or quadratic functions (next slide)
- Attrition:
  - 30% total attrition for no hiatus
  - 32% total attrition for 3 month hiatus
  - 34% total attrition for 6 month hiatus
  - 36% total attrition for 9 month hiatus
  - 38% total attrition for 12 month hiatus

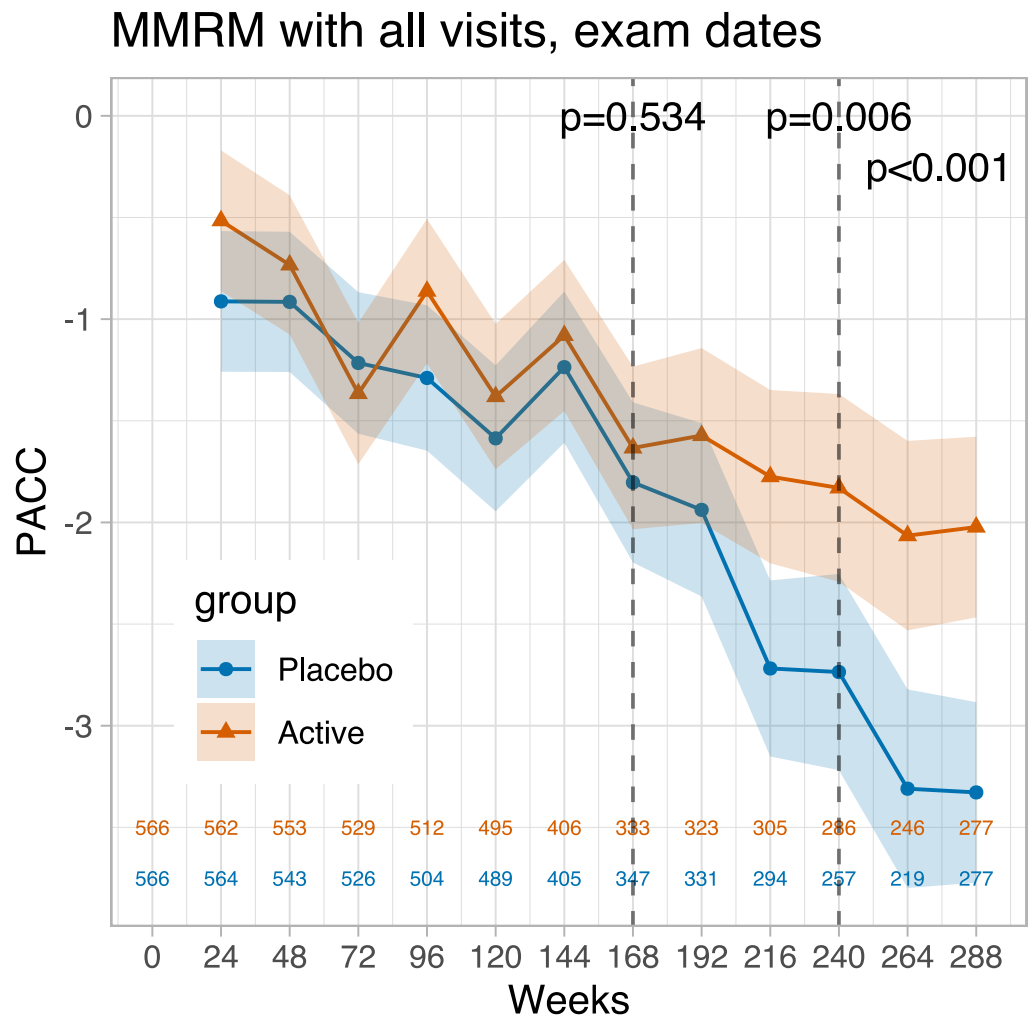
Assumed treatment effect over time



- Under no hiatus, assumes average week 240 benefit of about 0.73 PACC points (34% of HABS amyloid group difference).
- Residual standard deviation at week 240 about 4.0. (PACC as sum of 4 Z-scores)

Visit codes vs exam dates





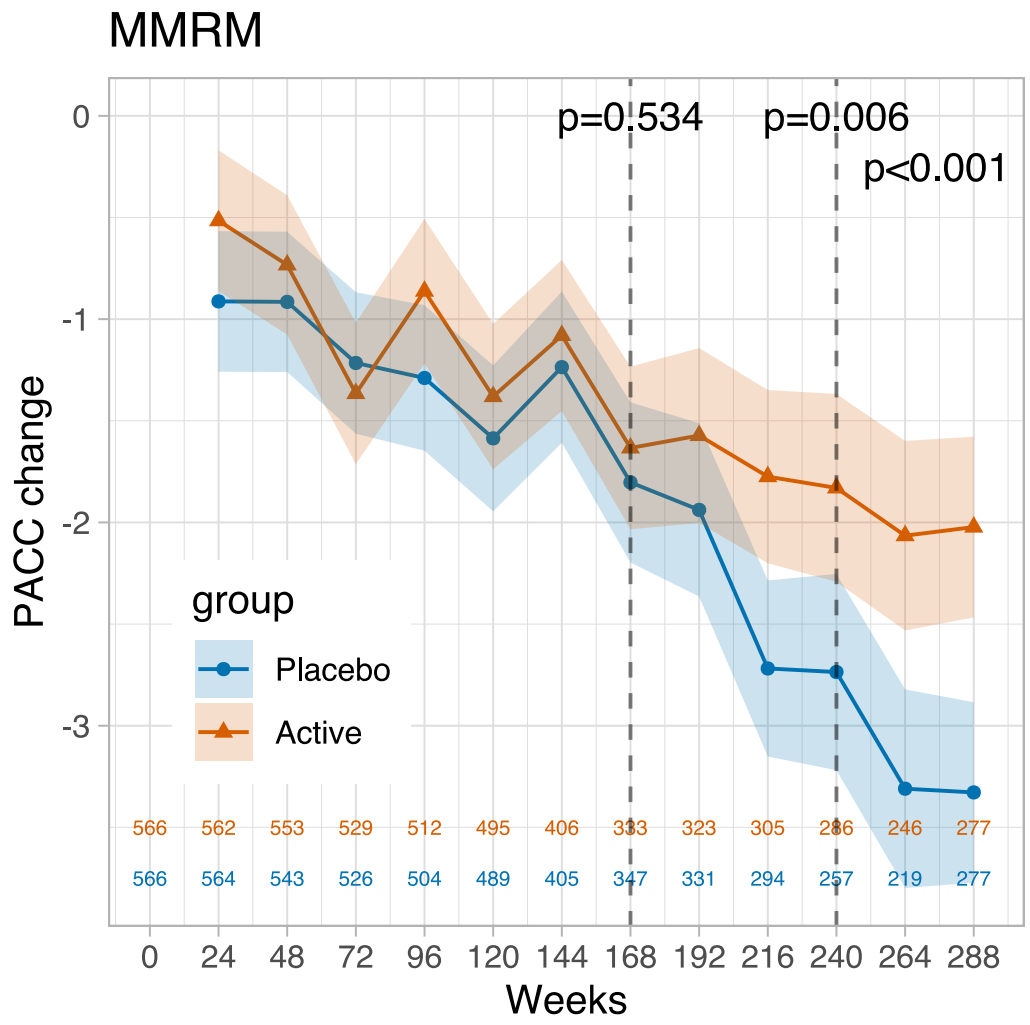
PACC test versions can get mixed together using exam dates

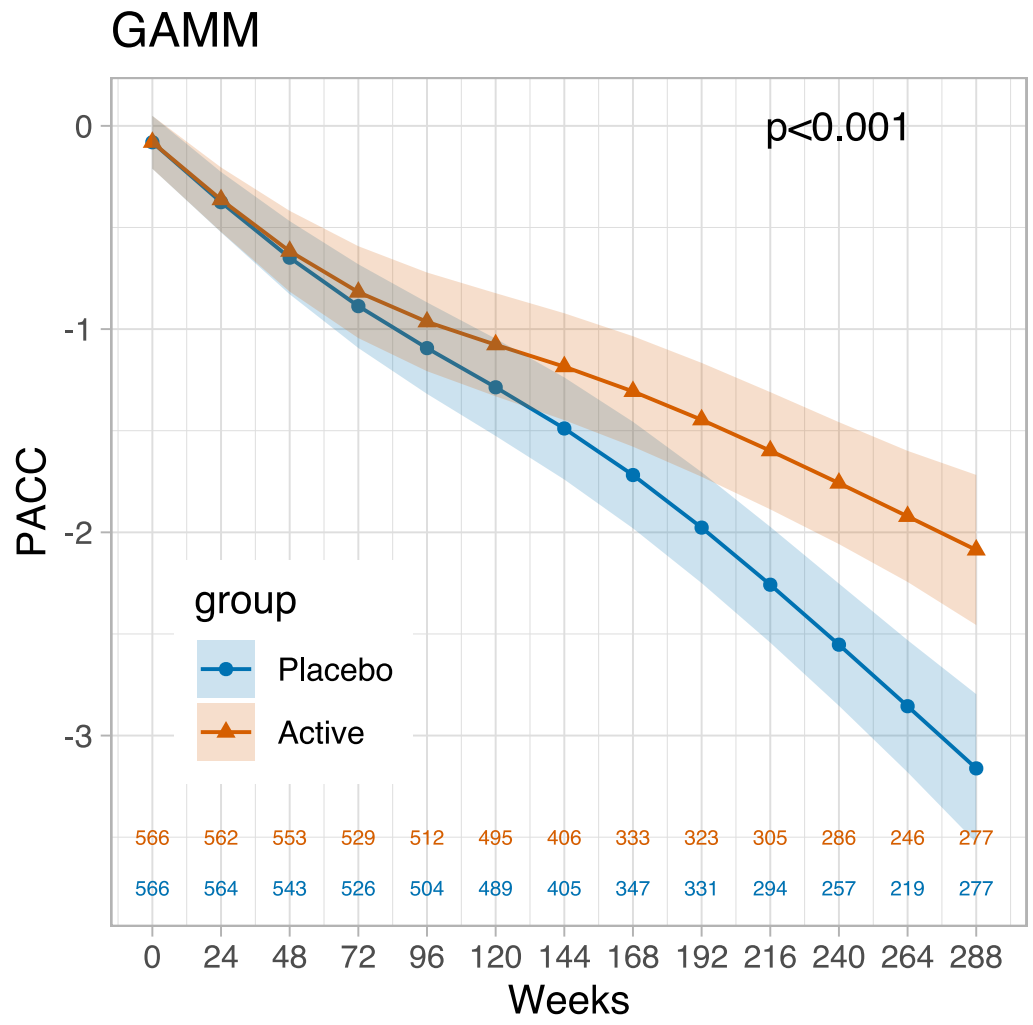
For example, with a 180 day hiatus, we might see these version counts:

	24	48	72	96	120	144	168	192	216	240	264
A	0	1096	0	1016	0	811	142	513	364	190	592
B	1126	0	1055	0	984	0	680	248	354	480	0

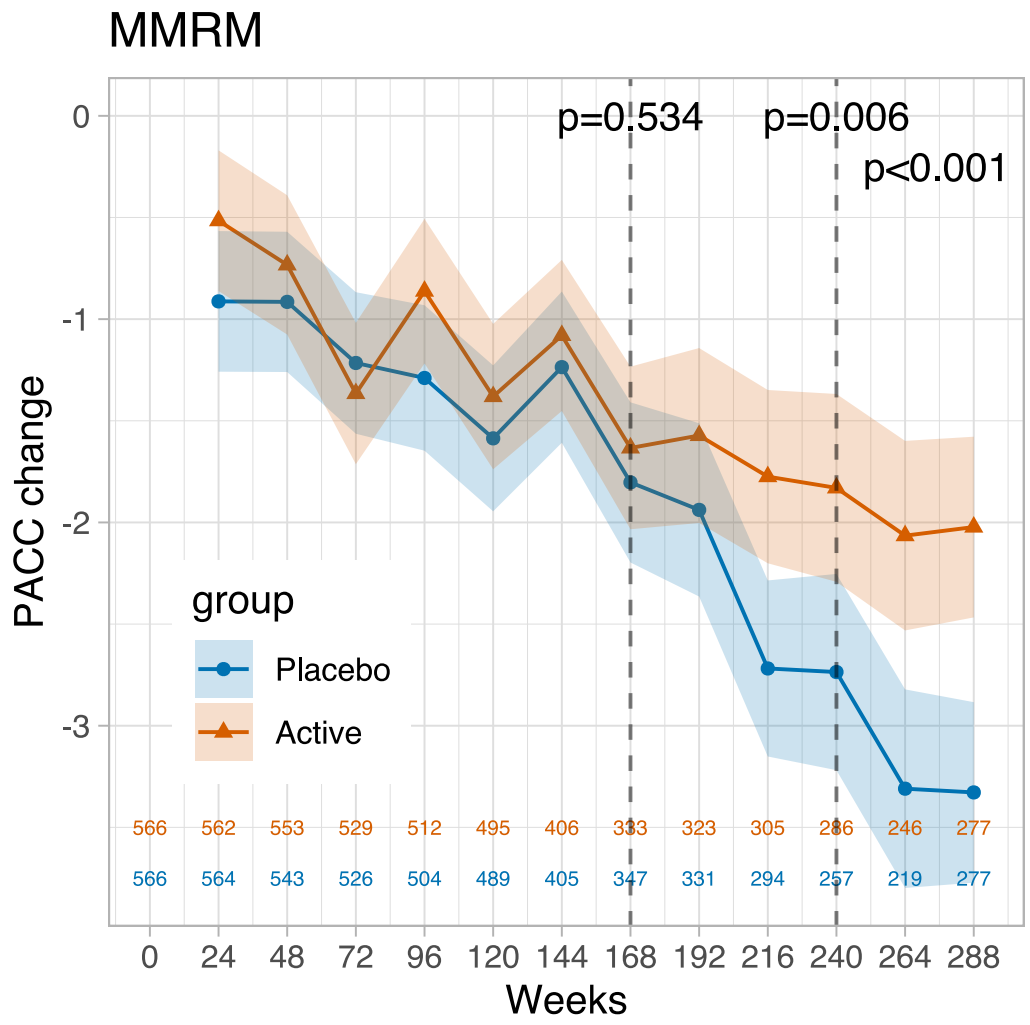
- With a categorical time analysis model, it would be awkward/difficult/impossible to control for version effects.
- With a continuous time analysis model, assuming a reasonable parametric mean structure over time, we can simply add a fixed effect for version.

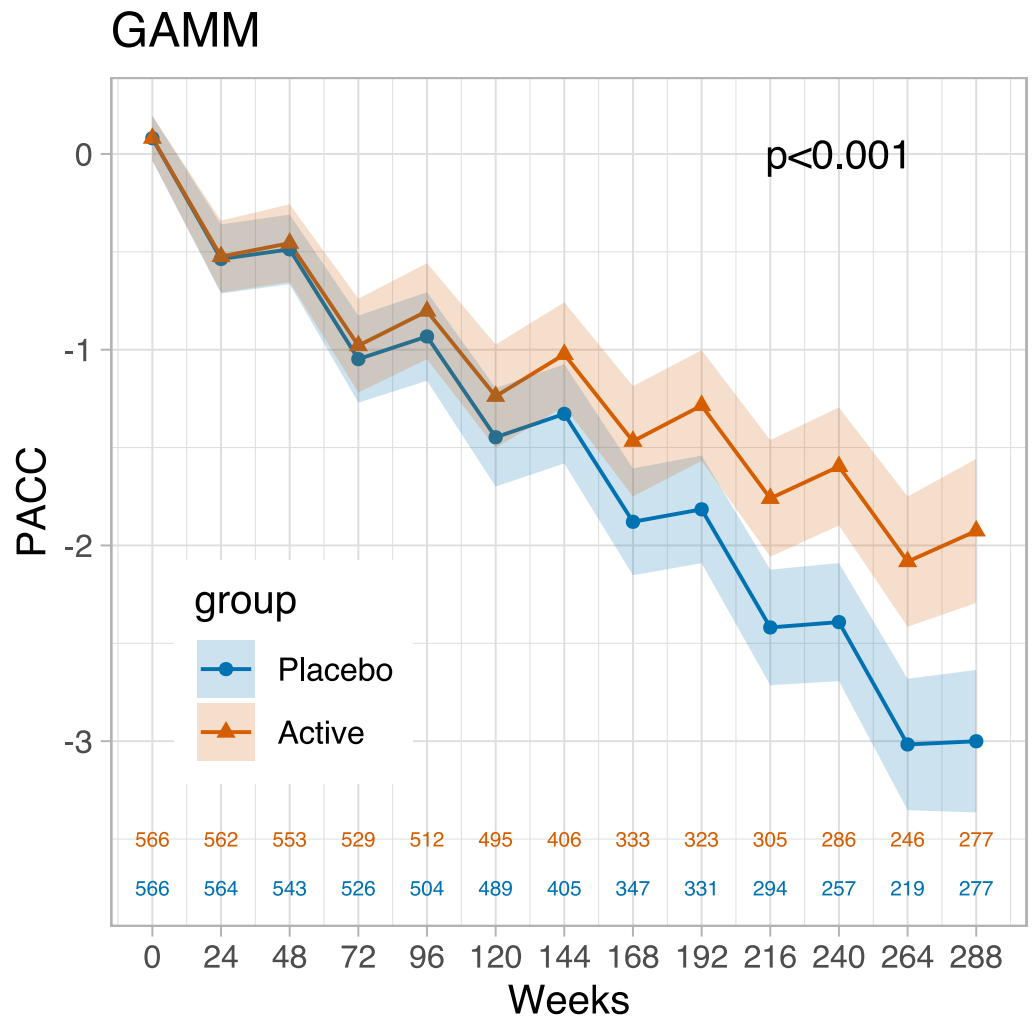
MMRM vs GAMM fit to simulated A4 data



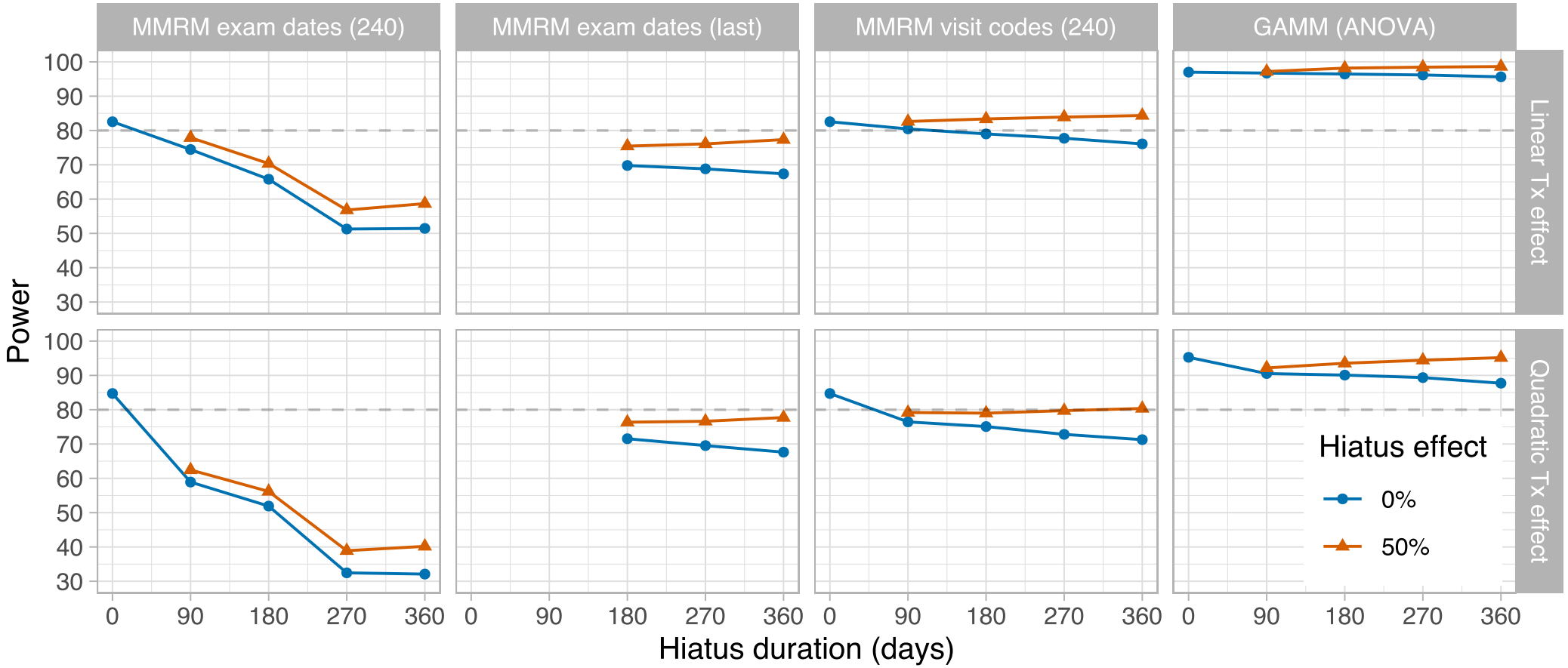


MMRM vs GAMM (representing version effect)





Power based on 1,000 simulated trials



GAMM is more powerful than MMRM and preserves power better with prolonged hiatus

Summary

- AIC chooses MMRM as the most predictive model in ADNI data, followed by Natural Cubic Spline, Quadratic, Hybrid, GAMM, and DPM approaches.
- The COVID-19 hiatus introduces some novel modeling issues for A4, and in particular, challenges for the MMRM framework.
- Regression splines are an attractive continuous time approach, with
  - Flexible assumptions about group trends over time
  - Adjustment for test version effects
- Under no hiatus, the GAMM approach with an ANOVA test for the main effect of treatment provides more power (95-97%) compared to MMRM timepoint-specific contrasts (82-85%)
- With a 90 day hiatus, the GAMM approach also provides more power (90-97%) compared to MMRM (59-82%). Difference grows with longer hiatuses.

Summary (continued)

- Type I error was well controlled for the main effect tests derived from GAMM in these scenarios, but more recent simulations have revealed some possible Type I error inflation.
- Natural Cubic Splines:
  - Might provide more reliable Type I error control
  - But they require pre-specifying knots
- Primary test?
  - Main effect or timepoint contrast?
  - Last timepoint? How do we ensure sufficient data?
  - Originally planned timepoint (week 240)?
  - Area between curves after week 240?
- Investigation continues. No decision to change A4 analysis plan has been made.

Thank you!

- Collaborators:
  - Gopalan Sethuraman, Oliver Langford, Rema Raman, Wenyi Lin, Philip Insel, Wesley K Thompson, Kathryn Papp, Reisa Sperling, Paul Aisen
  - Scott Andersen, Saptarshi Chatterjee, JonDavid Sparks, Michael Case, Thomas Jensen, Hong Liu-Seifert
- ADNI, HABS, and A4 study teams, investigators, and participants.

References

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