ADNI Neuroimaging Data Analysis Part 2: Following Baseline LMCI Patients

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Question: Do MCI patients in higher P(AD) bins have a worse cognitive outcome?

In this section, we investigate whether MCI (mild cognitive impairment) patients who had a higher predicted probability from the logistic regression trained on log transformed & scaled lipidomic/MRI data have a worse cognitive outcome. Recall that the predicted probabilities were binned into [0,0.2),[0.2-0.4),[0.4,0.6),[0.6,0.8),[0.8,1.0) bins for P(AD). Refer to Part 1 for more information.

We will be examining 5 different outcomes (4 ADNI specific, 1 MMSE) listed below. The ADNI specific scores range from -4 to 4 with higher being better. MMSE ranges from 0-30 with higher also being better. For MMSE, 20-24 is mild dementia, 13-20 is moderate, <13 is severe.

ADNI-MEM = ADNI memory score

ADNI-EF = ADNI executive function score

ADNI-LAN = ADNI language score

ADNI-VS = ADNI visuospatial ability score

MMSE = Mini Mental State Examination (30 questions)

However, in the case of MMSE, we will actually use the number of errors on the exam (30-MMSE) as the outcome in order to treat this as a discrete count to analyze.

The analysis will consist of looking at these metrics at baseline as well as their slopes longitudinally. We will perform pairwise constrasts between the 5 probability bins for each outcome $choose(5,2) = 10$, and with 5 outcomes at both baseline and longitudinal this leads to 100 tests in total. To account for multiple comparisons, we will use the Benjamini-Yekutieli False Discovery Rate (FDR) control method.

Data Preparation

Below, we preprocess the longitudinal data for analysis by joining it to the probabilities of AD for the MCI patients. Additionally, dates in the dataset are converted to times in years from baseline. The patients were followed approximately every 0.5 years (6 months) up until 11 years, at which point they were followed approximately yearly. Time will be treated continuously in the analyses later on since the exact timings are different per patient. Age and education years were also centered based on the full baseline data.

```
library(knitr)
library(dplyr)
library(tidyr)
library(readr)
library(stringr)
library(forcats)
library(lubridate)
library(ggplot2)
library(rlang)
library(purrr)

library(mgcv)
library(emmeans)

MCIdata = read_csv("MCIdata_withADprobs.csv")

rawlongdata = read_csv("ADNI_longitudinal.csv")

baseMCIprobdata = MCIdata %>% select(RID,ProbAD,BinAD)

unique(rawlongdata$VISCODE)
```

```
##  [1] "bl"   "m06"  "m102" "m108" "m120" "m126" "m132" "m144" "m36"  "m60"
## [11] "m66"  "m72"  "m78"  "m84"  "m90"  "m96"  "m12"  "m18"  "m24"  "m30"
## [21] "m48"  "m156" "m42"  "m54"  "m168" "m114"
```

```
vistimes = c(seq(0,132,6),144,156,168)
m = rep("m",length(vistimes))
visits_ordered = paste(m,vistimes,sep="")
visits_ordered[1] = "bl"
visits_ordered[2] = "m06"
visits_ordered
```

```
##  [1] "bl"   "m06"  "m12"  "m18"  "m24"  "m30"  "m36"  "m42"  "m48"  "m54"
## [11] "m60"  "m66"  "m72"  "m78"  "m84"  "m90"  "m96"  "m102" "m108" "m114"
## [21] "m120" "m126" "m132" "m144" "m156" "m168"
```

```
longdata = rawlongdata %>% mutate(VISCODE=as_factor(VISCODE),
                                  VISCODE = fct_relevel(VISCODE,visits_ordered),
                                  EXAMDATE = as_date(EXAMDATE,format="%m/%d/%Y"),
                                  APOE4 = as_factor(APOE4),
                                  revMMSE = 30-MMSE) %>% arrange(RID,VISCODE)

base_examdates = longdata %>% filter(VISCODE=="bl") %>% select(RID,EXAMDATE) %>%
  rename(BASEDATE=EXAMDATE)

longdata = longdata %>% inner_join(base_examdates,by="RID") %>%
  mutate(Time=time_length(EXAMDATE-BASEDATE,unit="years")) %>%
  relocate(BASEDATE,Time,.before=DX_bl)

longdata = longdata %>% mutate(AGE_CENTER = AGE-mean(AGE),
                               PTEDUCAT_CENTER = PTEDUCAT-mean(PTEDUCAT))

basedata = longdata %>% filter(VISCODE=="bl")

baseMCIdata = basedata %>% filter(DX_bl=="LMCI") %>% inner_join(baseMCIprobdata,by="RID") %>%
  mutate(BinAD=as_factor(BinAD),
         BinAD = fct_relevel(BinAD,"[0.0, 0.2)","[0.2, 0.4)","[0.4, 0.6)","[0.6, 0.8)","[0.8,
 1.0)"),
         RID = as_factor(RID))
```

Summary Stats for Demographics/Covariates and Cognitive Outcome in Full Baseline Data

Before proceeding to the main analysis we will first investigate some of the demographics in the full baseline dataset (including CN, AD, and LMCI patients).

```
basedata %>% group_by(DX_bl) %>% summarise(N=n(),meanAGE=mean(AGE),meanEDU=mean(PTEDUCAT),
                                           meanADNI_MEM = mean(ADNI_MEM),meanADNI_EF=mean
(ADNI_EF),
                                           meanADNI_LAN = mean(ADNI_LAN),meanADNI_VS=mean
(ADNI_VS),
                                            meanMMSE = mean(MMSE)) %>%
  kable(caption="Full Baseline Data Age, Education, and mean baseline cognitive measures")
```

Full Baseline Data Age, Education, and mean baseline cognitive measures

DX_bl	N	meanAGE	meanEDU	meanADNI_MEM	meanADNI_EF	meanADNI_LAN	meanADNI_VS	meanMMSE
AD	188	75.25851	14.65957	-0.8503883	-0.9679734	-0.7847766	-0.6115372	23.27660
CN	229	75.86943	16.06550	0.9754541	0.6475502	0.7751965	0.2351790	29.11354
LMCI	402	74.76144	15.64179	-0.0949328	-0.0490025	-0.0628532	-0.1348557	27.01493

From above, it is clear that patients with AD tend to score much lower in all the cognitive measures than both LMCI and CN, while LMCI scores in between. Age is approximately the same in all 3 groups and education years is only slightly lower for AD and MCI than CN.

```
kable(table(basedata$DX_bl,basedata$PTETHCAT),caption="Full Data: Baseline Diagnosis vs Ethnici
ty")
```

Full Data: Baseline Diagnosis vs Ethnicity

	Hisp/Latino	Not Hisp/Latino	Unknown
AD	4	182	2
CN	2	226	1
LMCI	13	386	3

```
kable(table(basedata$DX_bl,basedata$PTGENDER),caption="Full Data: Baseline Diagnosis vs Gender"
)
```

Full Data: Baseline Diagnosis vs Gender

	Female	Male
AD	89	99
CN	110	119
LMCI	143	259

```
kable(prop.table(table(baseMCIdata$BinAD,baseMCIdata$PTGENDER),1),caption="LMCI Data: AD Bin vs
Gender")
```

LMCI Data: AD Bin vs Gender

	Female	Male
[0.0, 0.2)	0.3200000	0.6800000
[0.2, 0.4)	0.3636364	0.6363636
[0.4, 0.6)	0.3818182	0.6181818
[0.6, 0.8)	0.2931034	0.7068966
[0.8, 1.0)	0.4024390	0.5975610

Most patients are not hispanic/latino, in all 3 categories, and thus we do not include ethnicity as a predictor. All 3 categories appear to have more males represented. Within the LMCI patients and the bins, the proportion of males and females is roughly the same across.

```
kable(prop.table(table(basedata$DX_bl,basedata$APOE4),1),caption="Full Data: Baseline Diagnosis
vs APOE4")
```

Full Data: Baseline Diagnosis vs APOE4

	0	1	2
AD	0.3404255	0.4680851	0.1914894
CN	0.7336245	0.2445415	0.0218341
LMCI	0.4651741	0.4179104	0.1169154

```
kable(prop.table(table(baseMCIdata$BinAD,baseMCIdata$APOE4),1),caption="LMCI Data: AD Bin vs APOE4")
```

LMCI Data: AD Bin vs APOE4

	0	1	2
[0.0, 0.2)	0.4960000	0.4000000	0.1040000
[0.2, 0.4)	0.4181818	0.4727273	0.1090909
[0.4, 0.6)	0.4909091	0.3454545	0.1636364
[0.6, 0.8)	0.3620690	0.4827586	0.1551724
[0.8, 1.0)	0.4756098	0.4268293	0.0975610

Presence of APOE4 allele is a known risk factor for AD, and it does appear that there is a greater proportion of patients with 1 or 2 APOE4 alleles in AD and LMCI vs CN. Within LMCI however, the proportion of patients with 1 or 2 APOE4 alleles does not appear to correlate with the bin.

Baseline Outcome Investigation

In this section, we examine each outcome at baseline. For the modeling, a Penalized GAM (Generalized Additive Model) from the mgcv package with spline terms (3 df) for continuous centered Age and Education is used in addition to linear terms. This is to adjust for possible nonlinearities in cognitive outcome vs age and education. Additionally, we include APOE4 main effect terms as well as up to a 3 factor interaction with centered Age and the P(AD) bin. This is to account for the fact that the effect of APOE4 may be different depending on the biochemical features used to construct the P(AD) bins, and may be different based on age. Similarly, the biochemical features may have a different impact depending on age as well.

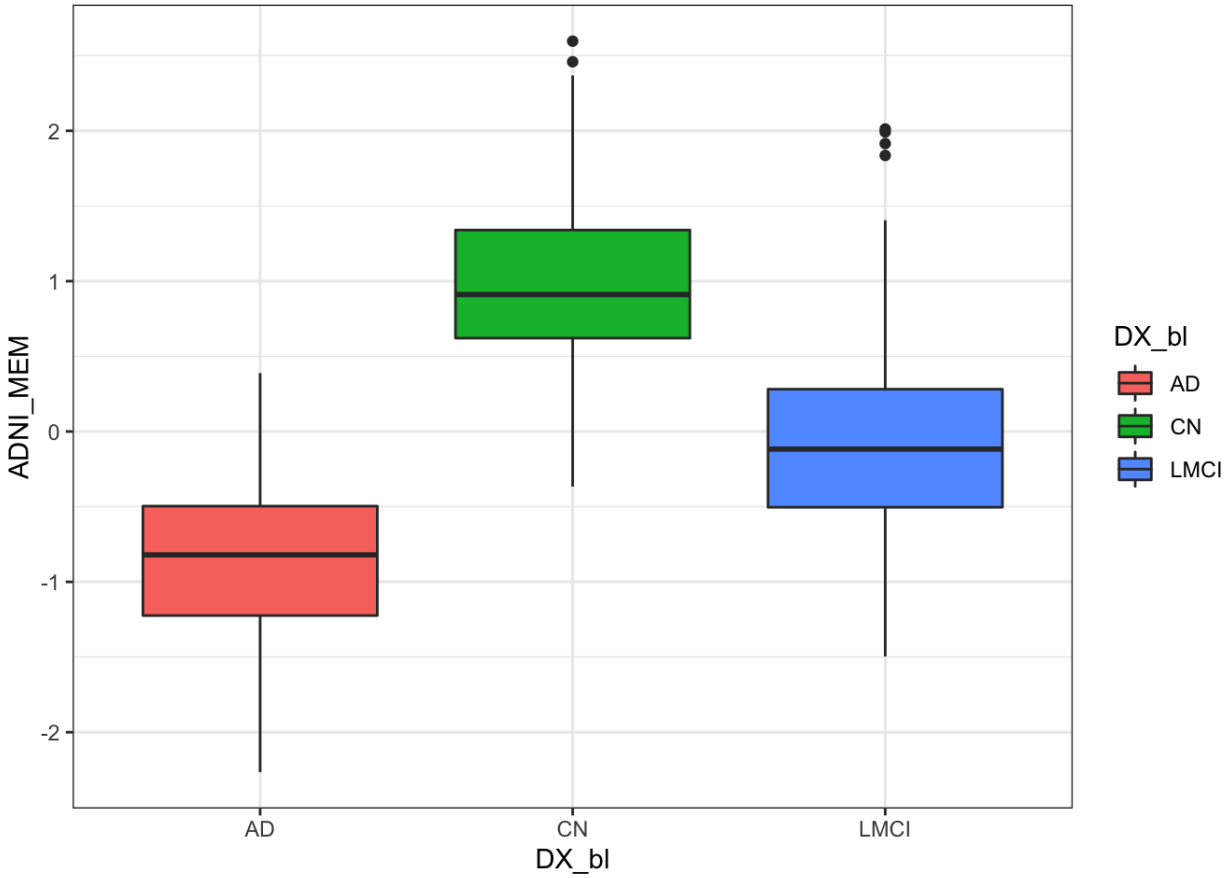
For each of the ADNI outcomes, a normal identity link GAM was used, while for MMSE it was converted to revMMSE=30-MMSE for use with a negative binomial GAM and log link.

This section will show the plots and baseline means for each cognitive outcome, pairwise contrasts/hypothesis testing will be done in the very end. Below is the wrapper function for the boxplots at baseline and the model fitting. For convenience to save time when knitting this document though, we load the models that were fitted outside of this document.

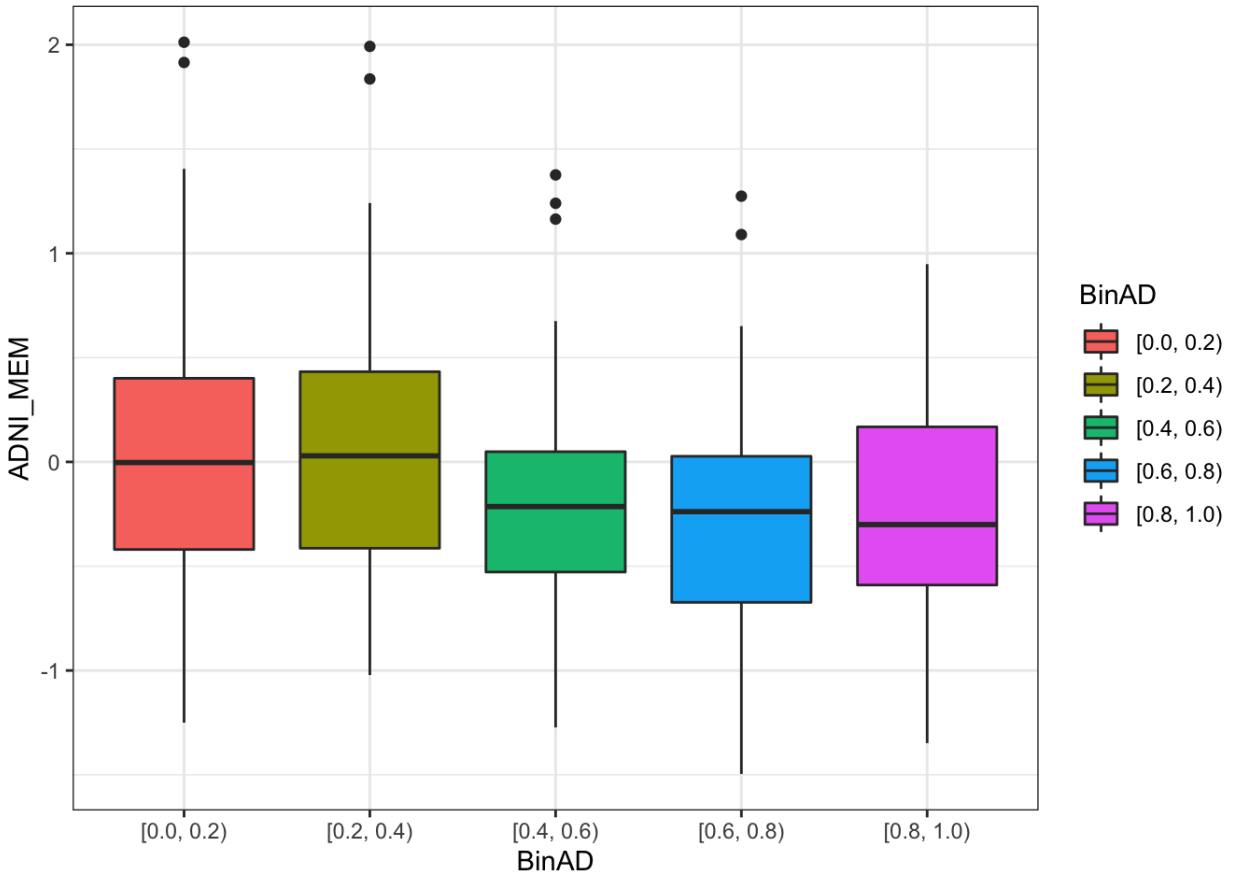
```
fit_baseline_GAM = function(response,data,family=gaussian(link=identity)){
  response = enexpr(response)
  data = enexpr(data)
  family=enexpr(family)
  model_call = expr(gam(!!response~PTGENDER+PTEDUCAT_CENTER+
                s(PTEDUCAT_CENTER,k=3)+s(AGE_CENTER,k=3)+AGE_CENTER*APOE4*BinAD,family=!!famil
y,data=!!data))
  model = eval_tidy(model_call,env=caller_env())
  return(model)

}

plot_baseline = function(data,response,group){
  response = enexpr(response)
  group = enexpr(group)
  p = ggplot(data,aes(x=!!group,y=!!response,fill=!!group)) + geom_boxplot() + theme_bw()
  return(p)
}
```

Baseline ADNI-MEM

```
ADNI_MEM_dxplot = plot_baseline(basedata,ADNI_MEM,DX_bl)
ADNI_MEM_binplot = plot_baseline(baseMCIdata,ADNI_MEM,BinAD)

ADNI_MEM_dxplot
```




```
ADNI_MEM_binplot
```




```
#Base_ADNI_MEM = fit_baseline_GAM(ADNI_MEM,baseMCIdata)
#saveRDS(Base_ADNI_MEM,file="Base_ADNI_MEM.rdata")
Base_ADNI_MEM = readRDS("Base_ADNI_MEM.rdata")
emm_MEM=emmeans(Base_ADNI_MEM,pairwise~BinAD,adjust="none")
comp_MEM = as_tibble(emm_MEM$contrasts) %>% mutate(response="ADNI_MEM",type="Baseline")

emm_MEM$emmeans %>% as_tibble() %>% kable(caption="Baseline ADNI-MEM by P(AD) bin")
```

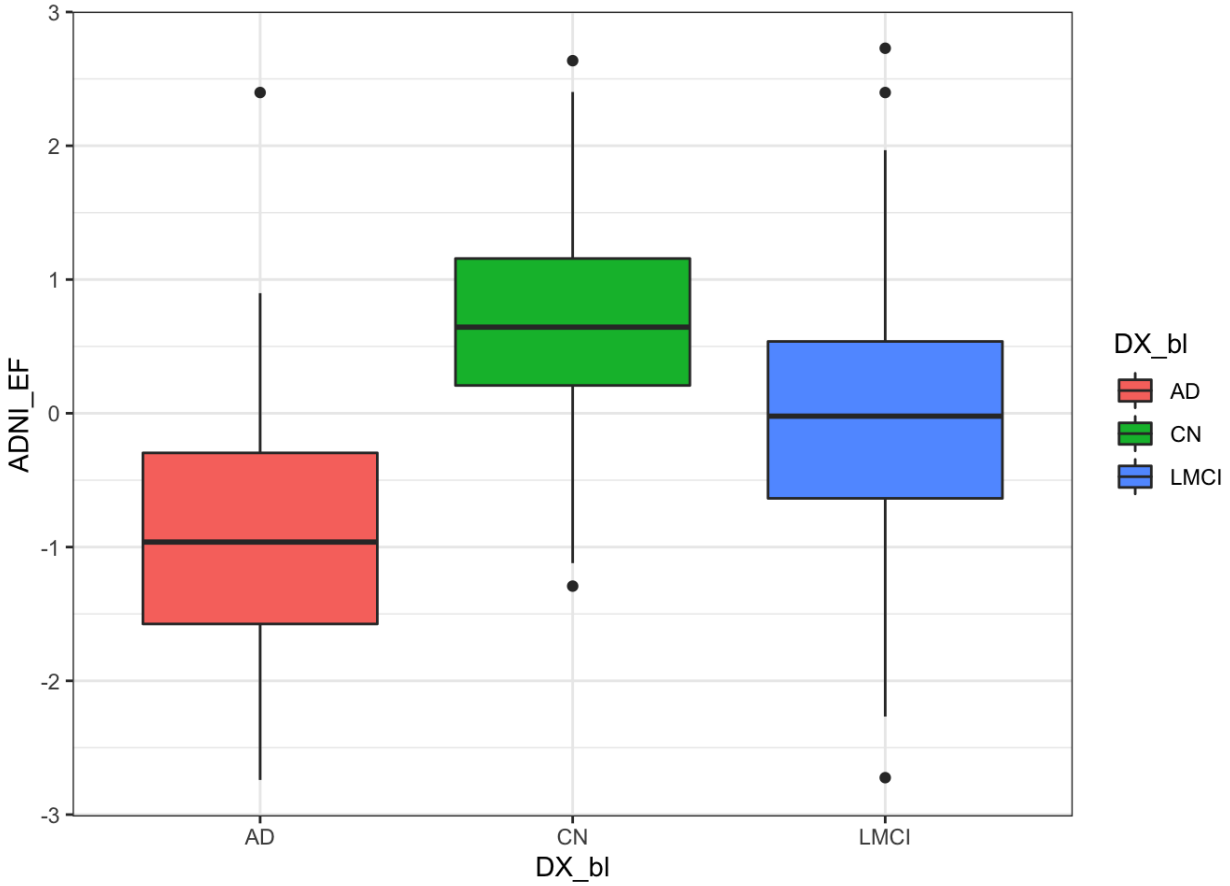
Baseline ADNI-MEM by P(AD) bin

BinAD	emmean	SE	df	lower.CL	upper.CL
[0.0, 0.2)	0.1075736	0.0763116	343	-0.0425241	0.2576713
[0.2, 0.4)	0.1148529	0.1038922	343	-0.0894932	0.3191990
[0.4, 0.6)	-0.2163895	0.1199055	343	-0.4522321	0.0194530
[0.6, 0.8)	-0.2742110	0.0889771	343	-0.4492204	-0.0992016
[0.8, 1.0)	-0.2558105	0.0834547	343	-0.4199579	-0.0916631

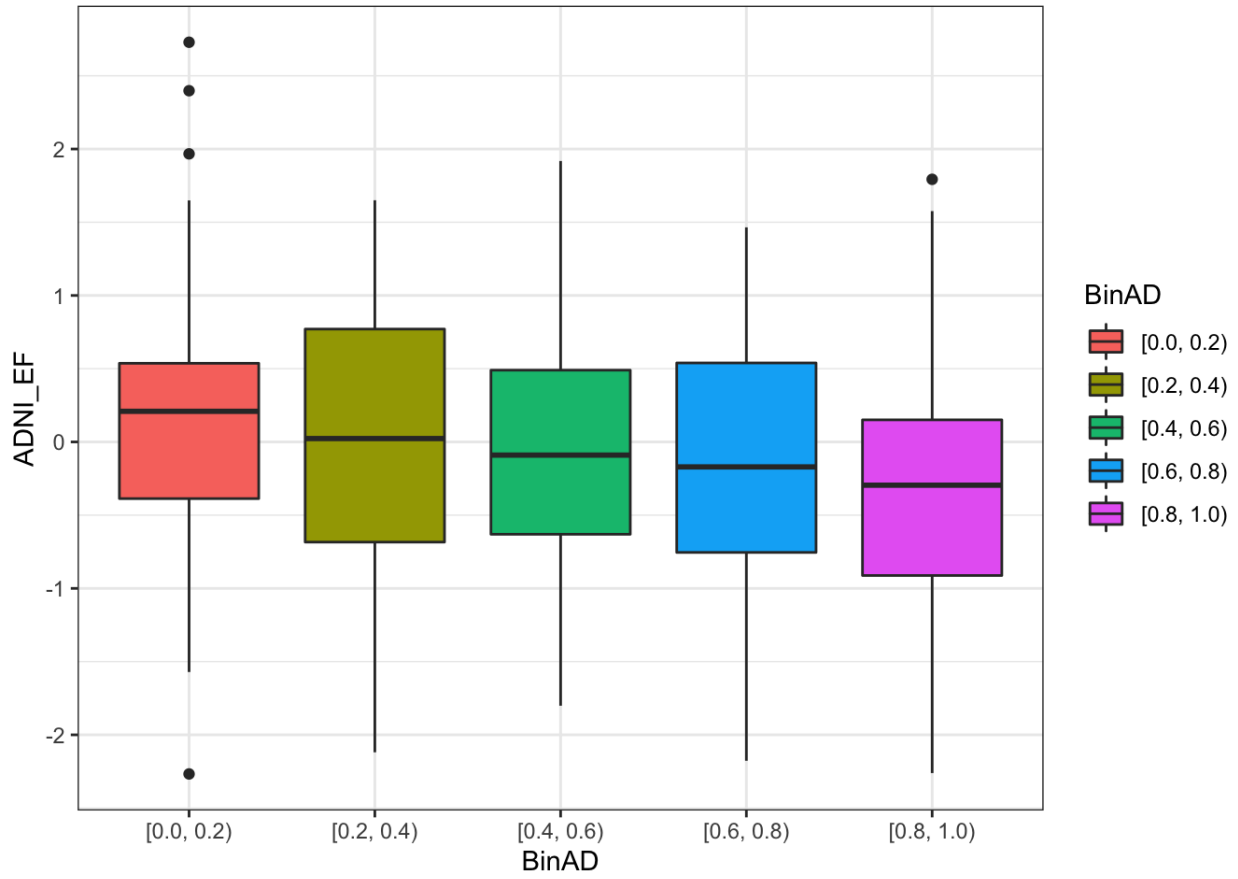
From the above, it appears that as the P(AD) bin increases, the mean memory functioning as assessed by ADNI-MEM tends to worsen (decrease). Note that corrected pairwise comparisons will be performed in the very end.

Baseline ADNI-EF

```
ADNI_EF_dxplot = plot_baseline(basedata,ADNI_EF,DX_bl)
ADNI_EF_binplot = plot_baseline(baseMCIdata,ADNI_EF,BinAD)

ADNI_EF_dxplot
```




```
ADNI_EF_binplot
```




```
#Base_ADNI_EF = fit_baseline_GAM(ADNI_EF,baseMCIdata)
#saveRDS(Base_ADNI_EF,file="Base_ADNI_EF.rdata")
Base_ADNI_EF = readRDS("Base_ADNI_EF.rdata")
emm_EF=emmeans(Base_ADNI_EF,pairwise~BinAD,adjust="none")
comp_EF = as_tibble(emm_EF$contrasts) %>% mutate(response="ADNI_EF",type="Baseline")

emm_EF$emmeans %>% as_tibble() %>% kable(caption="Baseline ADNI-EF by P(AD) bin")
```

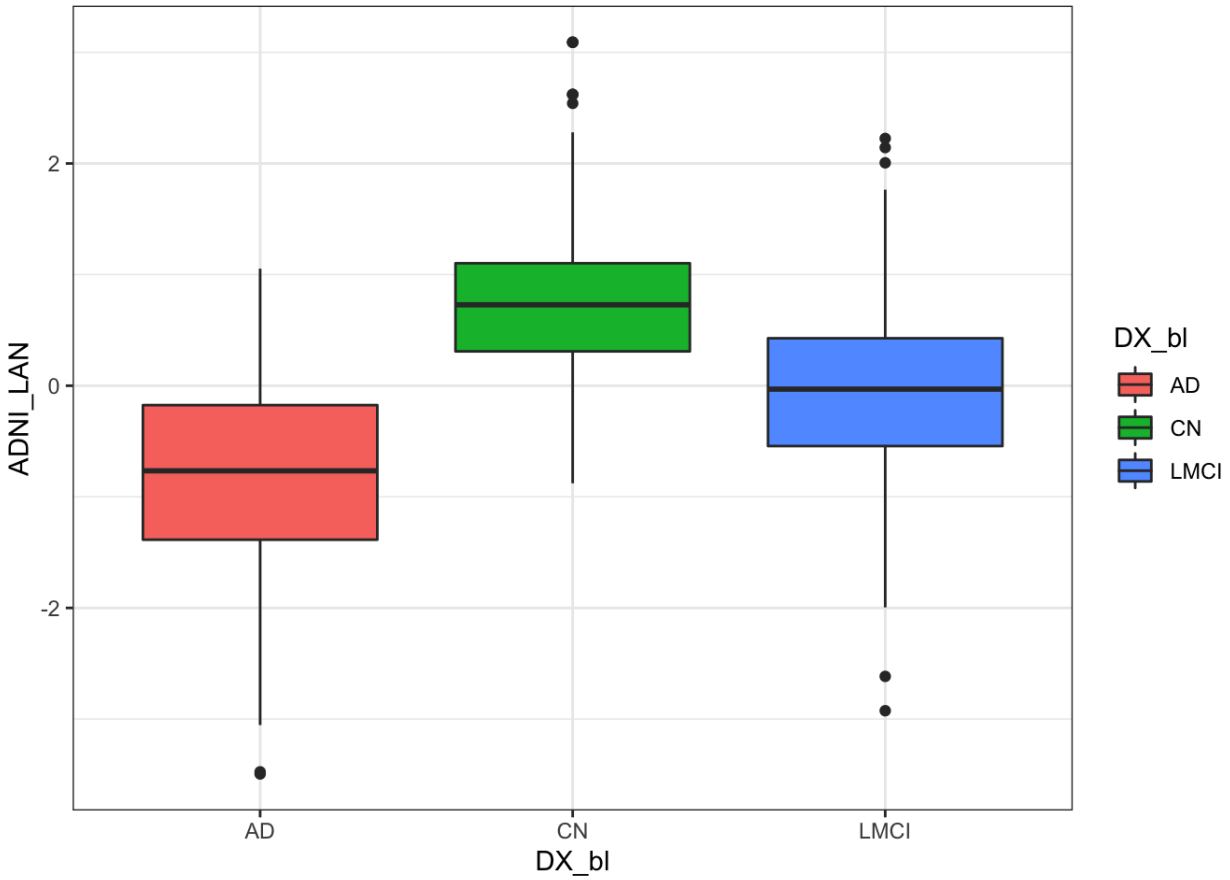
Baseline ADNI-EF by P(AD) bin

BinAD	emmean	SE	df	lower.CL	upper.CL
[0.0, 0.2)	0.0951823	0.1141065	341.8745	-0.1292569	0.3196215
[0.2, 0.4)	0.0955623	0.1532417	341.8745	-0.2058530	0.3969777
[0.4, 0.6)	-0.0377562	0.1739378	341.8745	-0.3798791	0.3043667
[0.6, 0.8)	-0.0683651	0.1306703	341.8745	-0.3253841	0.1886540
[0.8, 1.0)	-0.2215326	0.1238335	341.8745	-0.4651041	0.0220389

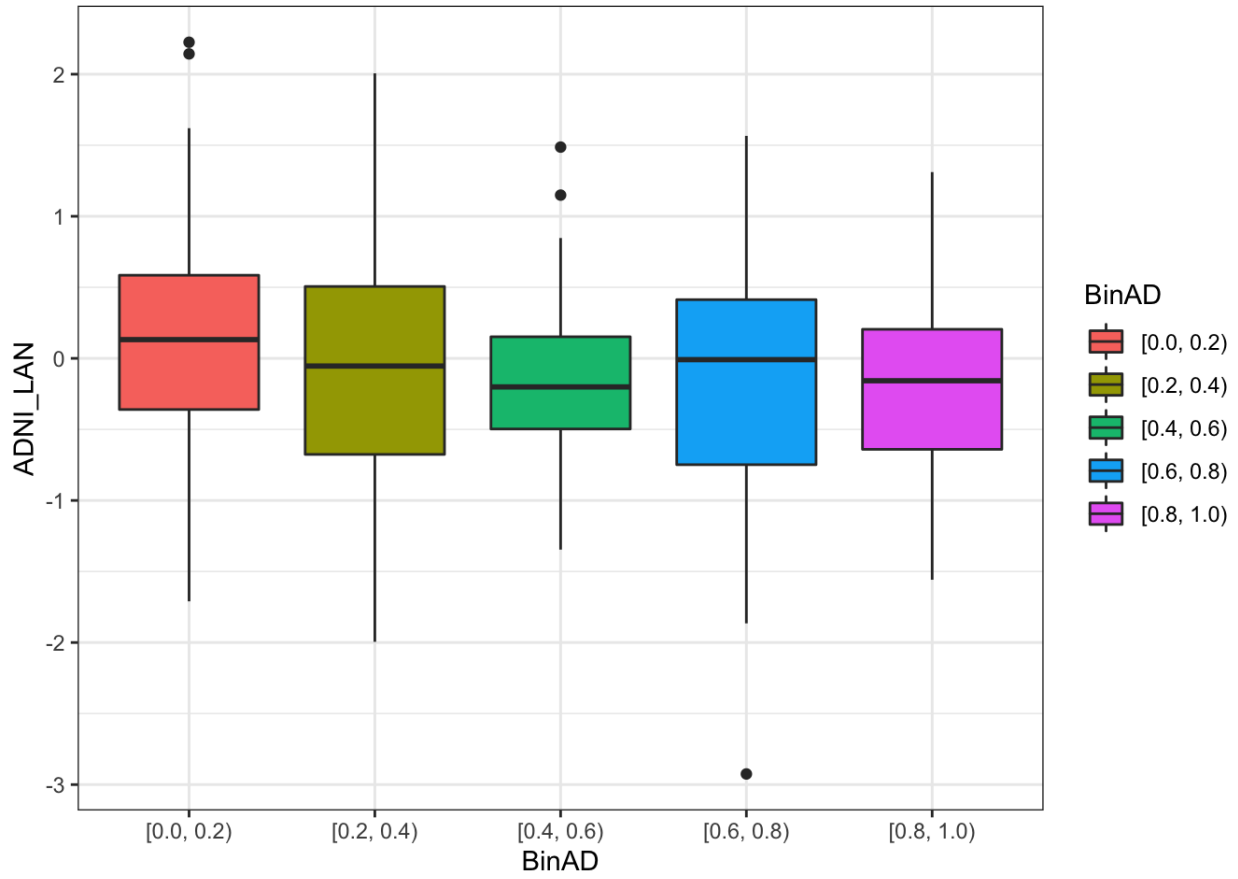
For executive functioning, the mean ADNI-EF worsens with increased P(AD) bin, with the greatest change going from the 0.6-0.8 bin to the 0.8-1.0 bin.

Baseline ADNI-LAN

```
ADNI_LAN_dxplot = plot_baseline(basedata,ADNI_LAN,DX_bl)
ADNI_LAN_binplot = plot_baseline(baseMCIdata,ADNI_LAN,BinAD)

ADNI_LAN_dxplot
```




```
ADNI_LAN_binplot
```




```
#Base_ADNI_LAN = fit_baseline_GAM(ADNI_LAN,baseMCIdata)
#saveRDS(Base_ADNI_LAN,file="Base_ADNI_LAN.rdata")
Base_ADNI_LAN = readRDS("Base_ADNI_LAN.rdata")
emm_LAN=emmeans(Base_ADNI_LAN,pairwise~BinAD,adjust="none")
comp_LAN = as_tibble(emm_LAN$contrasts) %>% mutate(response="ADNI_LAN",type="Baseline")

emm_LAN$emmeans %>% as_tibble() %>% kable(caption="Baseline ADNI-LAN by P(AD) bin")
```

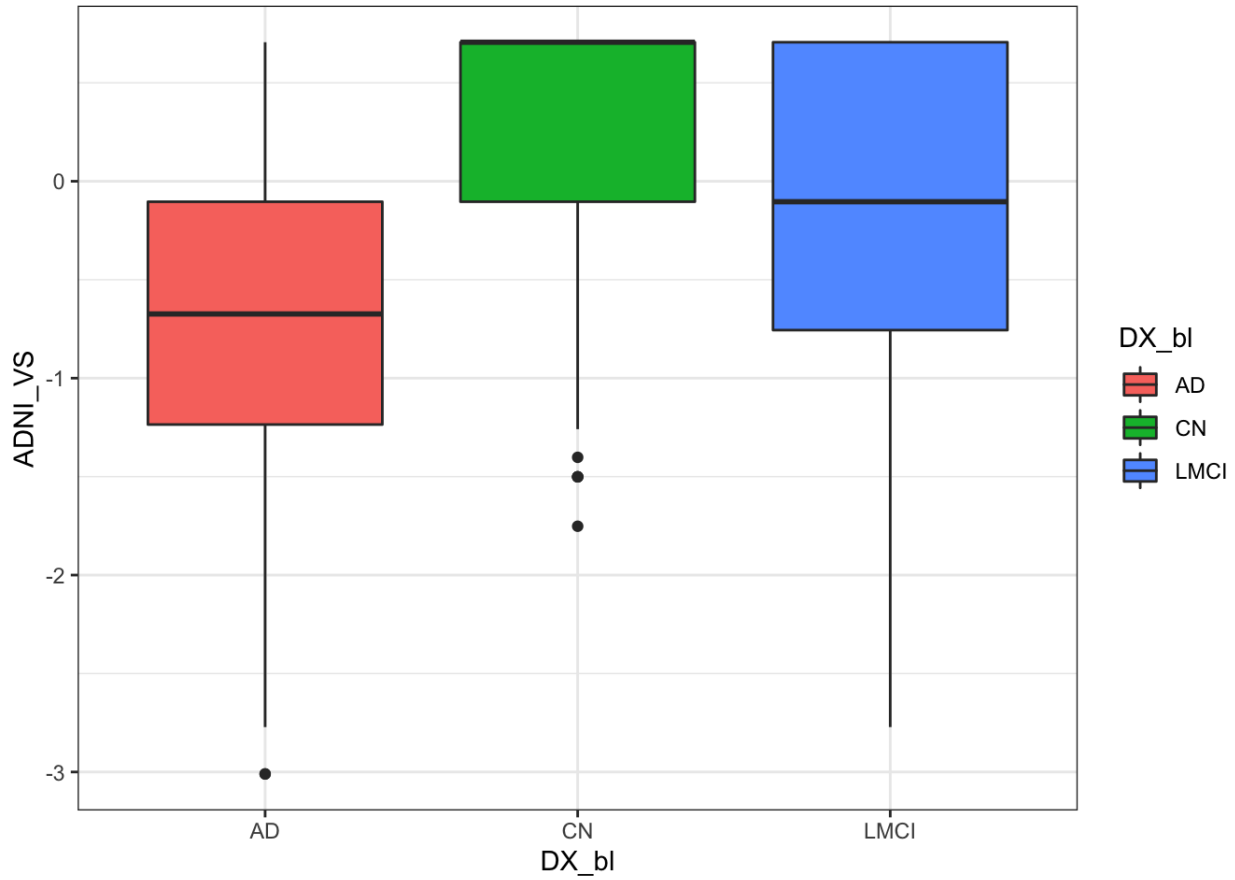
Baseline ADNI-LAN by P(AD) bin

BinAD	emmean	SE	df	lower.CL	upper.CL
[0.0, 0.2)	0.1495863	0.1013304	342.2138	-0.0497224	0.3488950
[0.2, 0.4)	-0.0466102	0.1354065	342.2138	-0.3129440	0.2197236
[0.4, 0.6)	-0.0423912	0.1557431	342.2138	-0.3487254	0.2639431
[0.6, 0.8)	-0.0895592	0.1164400	342.2138	-0.3185874	0.1394689
[0.8, 1.0)	-0.1648441	0.1100319	342.2138	-0.3812680	0.0515799

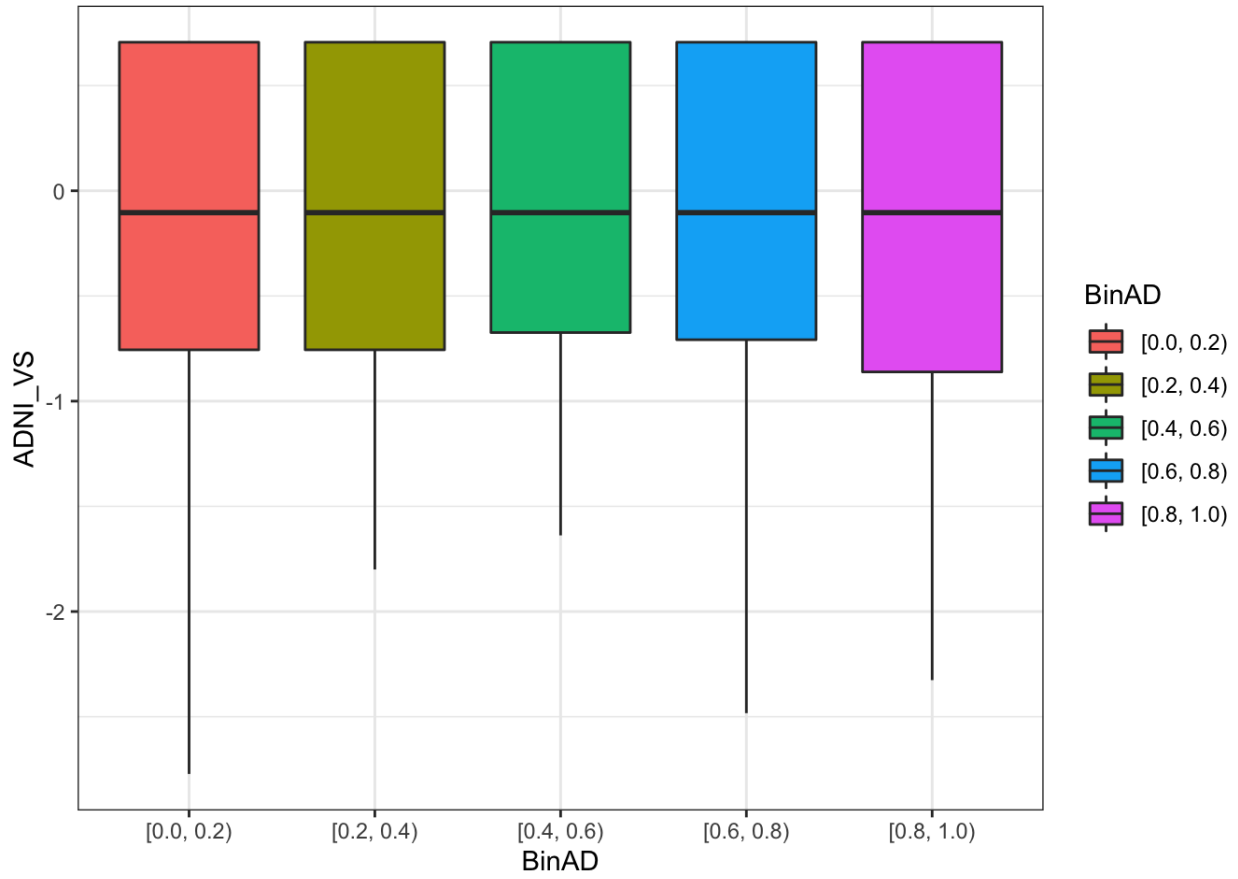
A similar trend is seen in ADNI-LAN, but here the greatest change occurs from the lowest bin [0,0.2) to [0.2,0.4) and from [0.6,0.8) to [0.8,1.0). Overall, it does appear that the predicted probability from the lipid/MRI features correlate to the cognitive outcome.

Baseline ADNI-VS

```
ADNI_VS_dxplot = plot_baseline(basedata,ADNI_VS,DX_bl)
ADNI_VS_binplot = plot_baseline(baseMCIdata,ADNI_VS,BinAD)

ADNI_VS_dxplot
```




```
ADNI_VS_binplot
```




```
#Base_ADNI_VS = fit_baseline_GAM(ADNI_VS,baseMCIdata)
#saveRDS(Base_ADNI_VS,file="Base_ADNI_VS.rdata")
Base_ADNI_VS = readRDS("Base_ADNI_VS.rdata")
emm_VS = emmeans(Base_ADNI_VS,pairwise~BinAD,adjust="none")
```

```
## NOTE: Results may be misleading due to involvement in interactions
```

```
comp_VS = as_tibble(emm_VS$contrasts) %>% mutate(response="ADNI_VS",type="Baseline")

emm_VS$emmeans %>% as_tibble() %>% kable(caption="Baseline ADNI-VS by P(AD) bin")
```

Baseline ADNI-VS by P(AD) bin

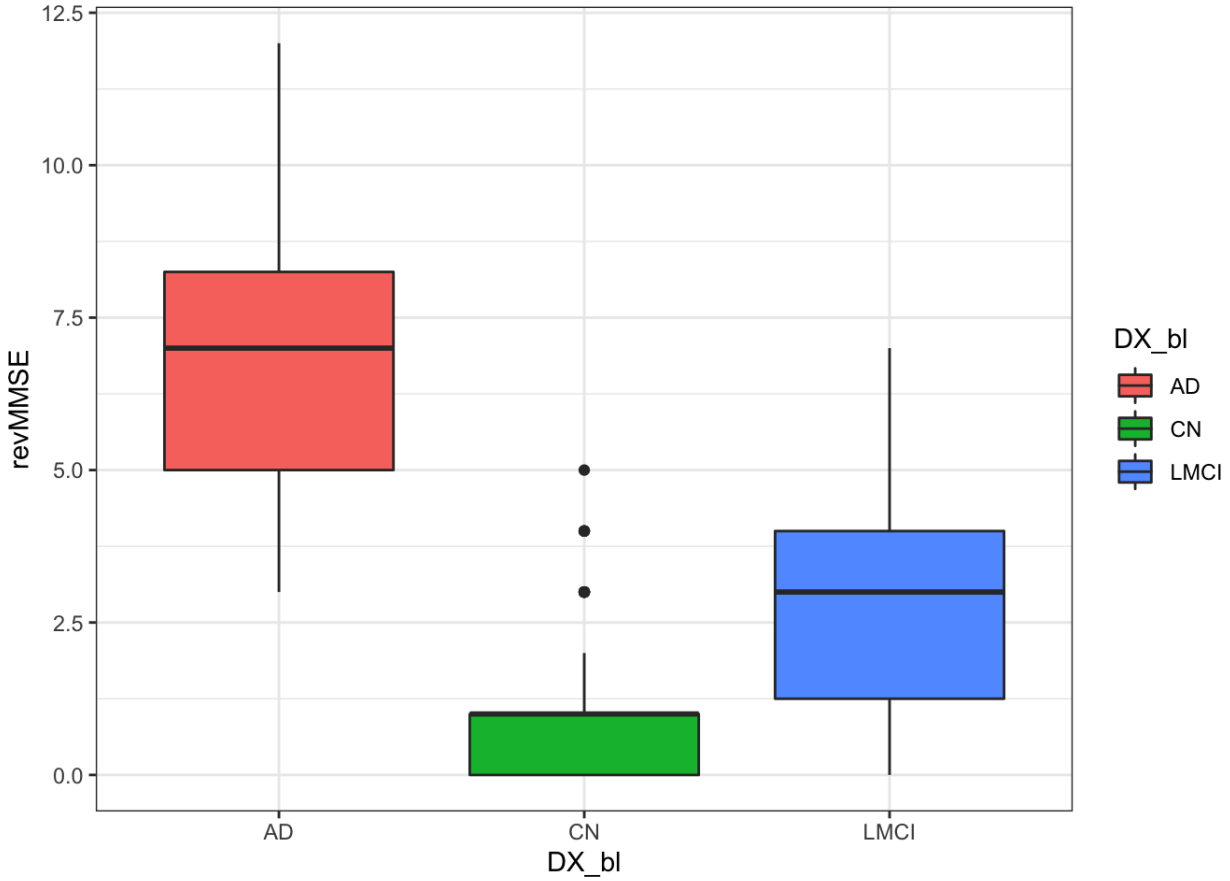
BinAD	emmean	SE	df	lower.CL	upper.CL
[0.0, 0.2)	-0.0767119	0.1065953	342.0023	-0.2863768	0.1329530
[0.2, 0.4)	-0.1245636	0.1444108	342.0023	-0.4086088	0.1594815
[0.4, 0.6)	0.1142605	0.1630914	342.0023	-0.2065280	0.4350490
[0.6, 0.8)	-0.1843773	0.1224788	342.0023	-0.4252839	0.0565293
[0.8, 1.0)	-0.1656622	0.1159300	342.0023	-0.3936878	0.0623633

In the case of visuopatial functioning, things are less clear. There is a slight trend from the lowest group to the highest group but it is not very strong.

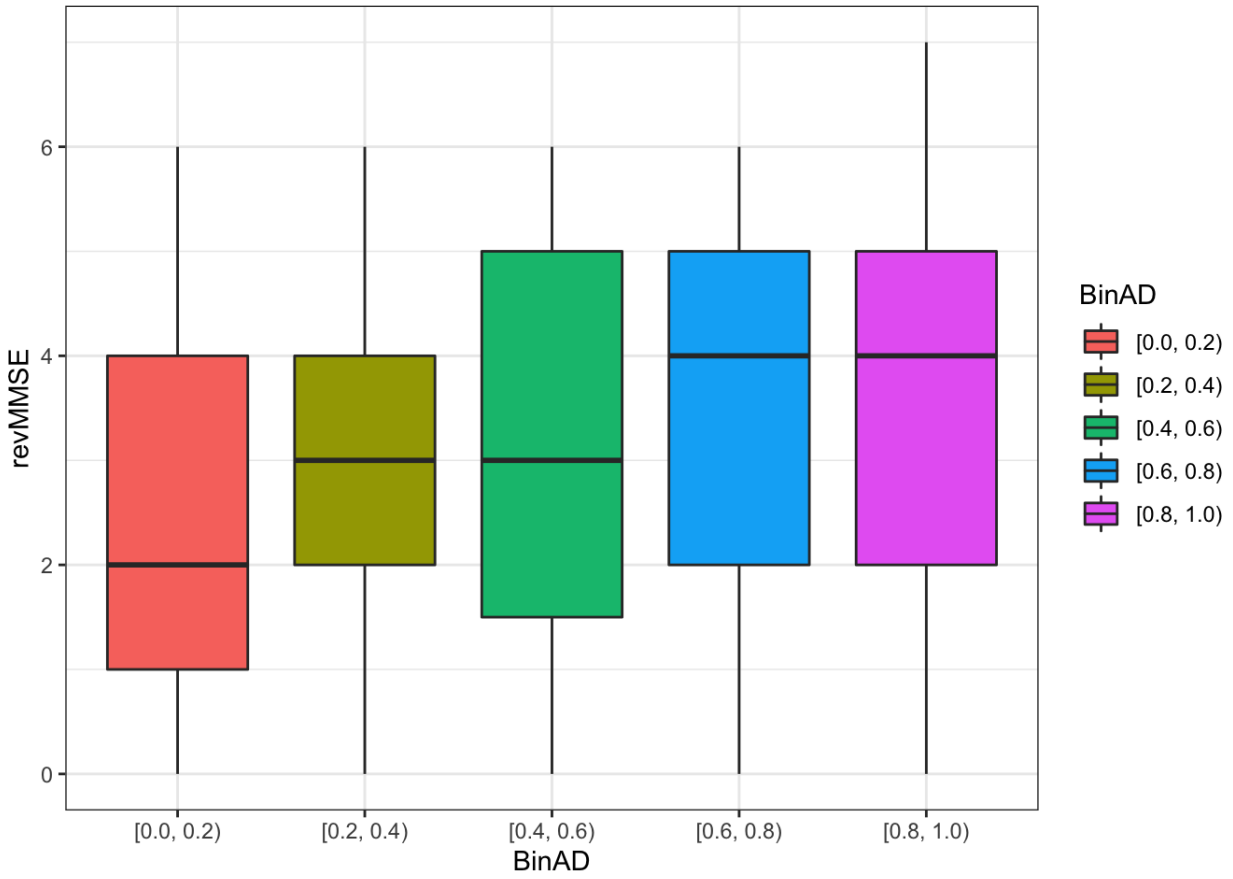
Baseline MMSE Errors

Note the below is actually the number of errors on the MMSE exam, so higher is WORSE. And in this case, a negative binomial GAM is used to model the count data.

```
revMMSE_dxplot = plot_baseline(basedata,revMMSE,DX_bl)
revMMSE_binplot = plot_baseline(baseMCIdata,revMMSE,BinAD)

revMMSE_dxplot
```




```
revMMSE_binplot
```




```
#Base_revMMSE = fit_baseline_GAM(revMMSE,baseMCIdata,family = nb(link=log))
#saveRDS(Base_revMMSE,file="Base_revMMSE.rdata")
Base_revMMSE = readRDS("Base_revMMSE.rdata")
emm_revMMSE = emmeans(Base_revMMSE,pairwise~BinAD,transform="response",adjust="none")
```

```
## NOTE: Results may be misleading due to involvement in interactions
```

```
comp_revMMSE = as_tibble(emm_revMMSE$contrasts) %>% mutate(response="revMMSE",type="Baseline")

emm_revMMSE$emmeans %>% as_tibble() %>% kable(caption="Baseline MMSE errors vs P(AD) bin")
```

Baseline MMSE errors vs P(AD) bin

BinAD	response	SE	df	lower.CL	upper.CL
[0.0, 0.2)	2.380786	0.2051938	342.3745	1.977187	2.784385
[0.2, 0.4)	3.137294	0.3536090	342.3745	2.441774	3.832813
[0.4, 0.6)	3.056579	0.3923276	342.3745	2.284903	3.828254
[0.6, 0.8)	3.638799	0.3143074	342.3745	3.020582	4.257015
[0.8, 1.0)	3.316819	0.2892815	342.3745	2.747826	3.885811

The number of errors on baseline MMSE does appear to increase with the bin from about 2 to 3-4, although the trend is weak at baseline.

Overall, we see that the bins do correlate with worsening cognitive outcome in terms of the means, but it remains to see (after the next longitudinal section) which trends are statistically significant (accounting for multiple comparisons)

Longitudinal Outcome Investigation

In this section, we examine the binned LMCI patients over time and compare the rate of change of their cognition metrics per year.

The model used here is a Penalized Mixed GAM with terms similar to above, except this time including random effects intercept and time slope for the RID,linear and spline (df=3) terms for centered age, centered education years as well as up to a 4 factor interaction of time with centered age, APOE4,and bin.

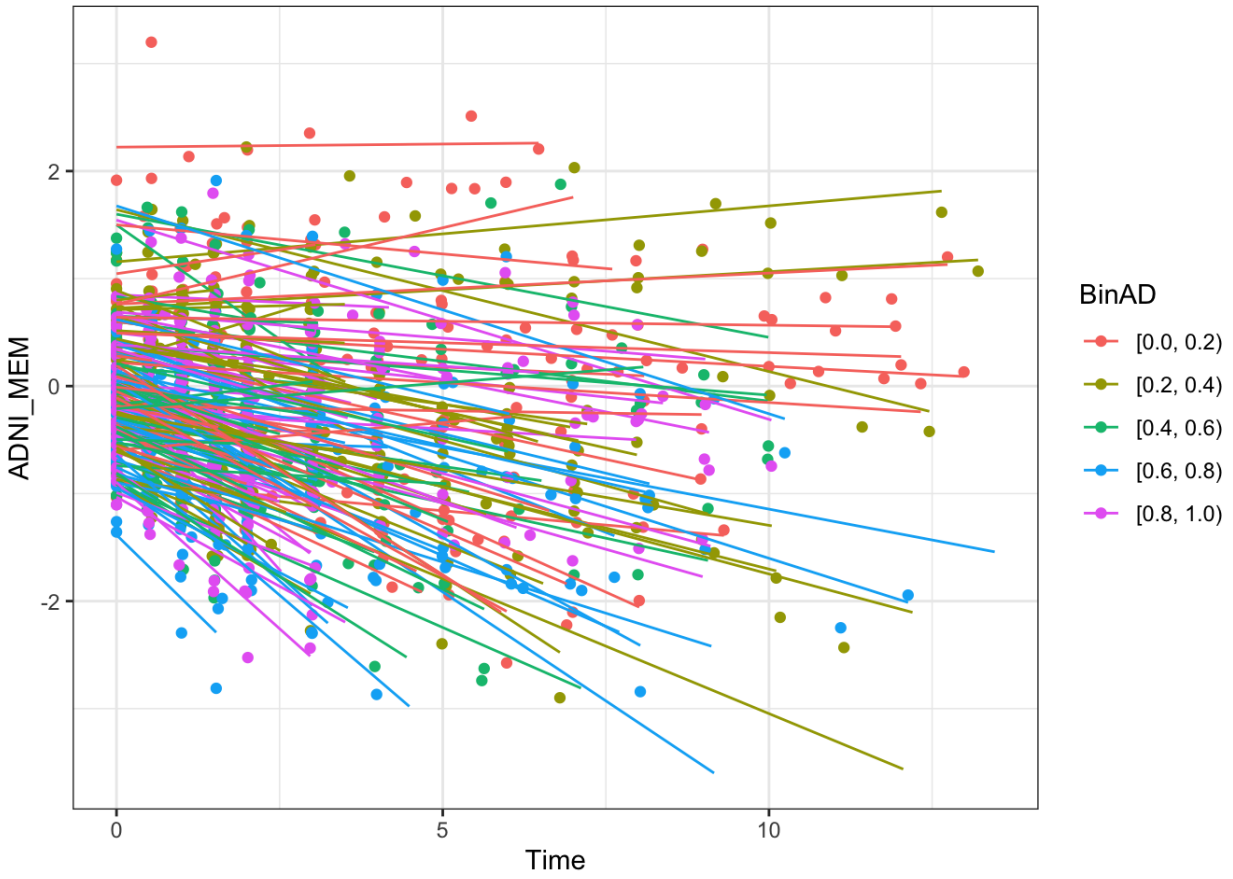
Following this section, we will perform the FDR corrected multiple comparisons for 100 tests across all the outcomes including the baseline ones.

Note that the plots in this section display the fitted LMM per RID, and only for 35 sampled RIDs per group so as to avoid cluttering the plot.

```
longMCIdata = longdata %>% filter(DX_bl=="LMCI") %>% inner_join(baseMCIprobdata,by="RID") %>%
  mutate(BinAD=as_factor(BinAD),
         BinAD = fct_relevel(BinAD,"[0.0, 0.2)","[0.2, 0.4)","[0.4, 0.6)","[0.6, 0.8)","[0.8,
 1.0)"),
         RID = as_factor(RID))


fit_longitudinal_GAM = function(response,data,family=gaussian(link=identity)){
  response = enexpr(response)
  data = enexpr(data)
  family = enexpr(family)
  model_call = expr(gam(!!response~s(RID,bs="re")+s(RID,Time,bs="re")+PTGENDER+PTEDUCAT_CENTER+
s(PTEDUCAT_CENTER,k=3)+
                          s(AGE_CENTER,k=3)+AGE_CENTER*APOE4*BinAD*Time,family=!!family,data=!!
data))
  model = eval_tidy(model_call,env=caller_env())
  return(model)
}

plot_longitudinal_samples = function(data,model,n_pergroup){

  sampdata = data %>% group_by(RID,BinAD) %>% nest() %>% group_by(BinAD) %>%
    slice_sample(n=n_pergroup) %>% unnest(cols=c(data))

  response = str_trim(str_split(deparse(formula(model))[1],"~")[[1]][1])
  new_response = paste(response,"_hat",sep="")

  sampdata[[new_response]] = predict(model,sampdata)

  response = as.symbol(response)
  new_response = as.symbol(new_response)

  p = ggplot(sampdata,aes(x=Time,y=!!response,group=RID,col=BinAD)) +
    geom_point() + geom_line(inherit.aes=FALSE,aes(x=Time,y=!!new_response,group=RID,col=BinA
D)) +
    theme_bw()

  return(p)
}
```

Longitudinal ADNI-MEM

```
#LMM_ADNI_MEM = fit_longitudinal_GAM(ADNI_MEM,longMCIdata)
#saveRDS(LMM_ADNI_MEM,file="LMM_ADNI_MEM.rdata")
LMM_ADNI_MEM = readRDS("LMM_ADNI_MEM.rdata")
emm_long_MEM = emtrends(LMM_ADNI_MEM,pairwise~BinAD,var="Time",adjust="none")
comps_long_MEM = as_tibble(emm_long_MEM$contrasts) %>% mutate(response="ADNI_MEM",type="TimeSlo
pe")

set.seed(100)
plot_longitudinal_samples(longMCIdata,LMM_ADNI_MEM,35)
```




```
emm_long_MEM$emtrends %>% as_tibble() %>% kable(caption="Slope of ADNI-MEM over time (yr)")
```

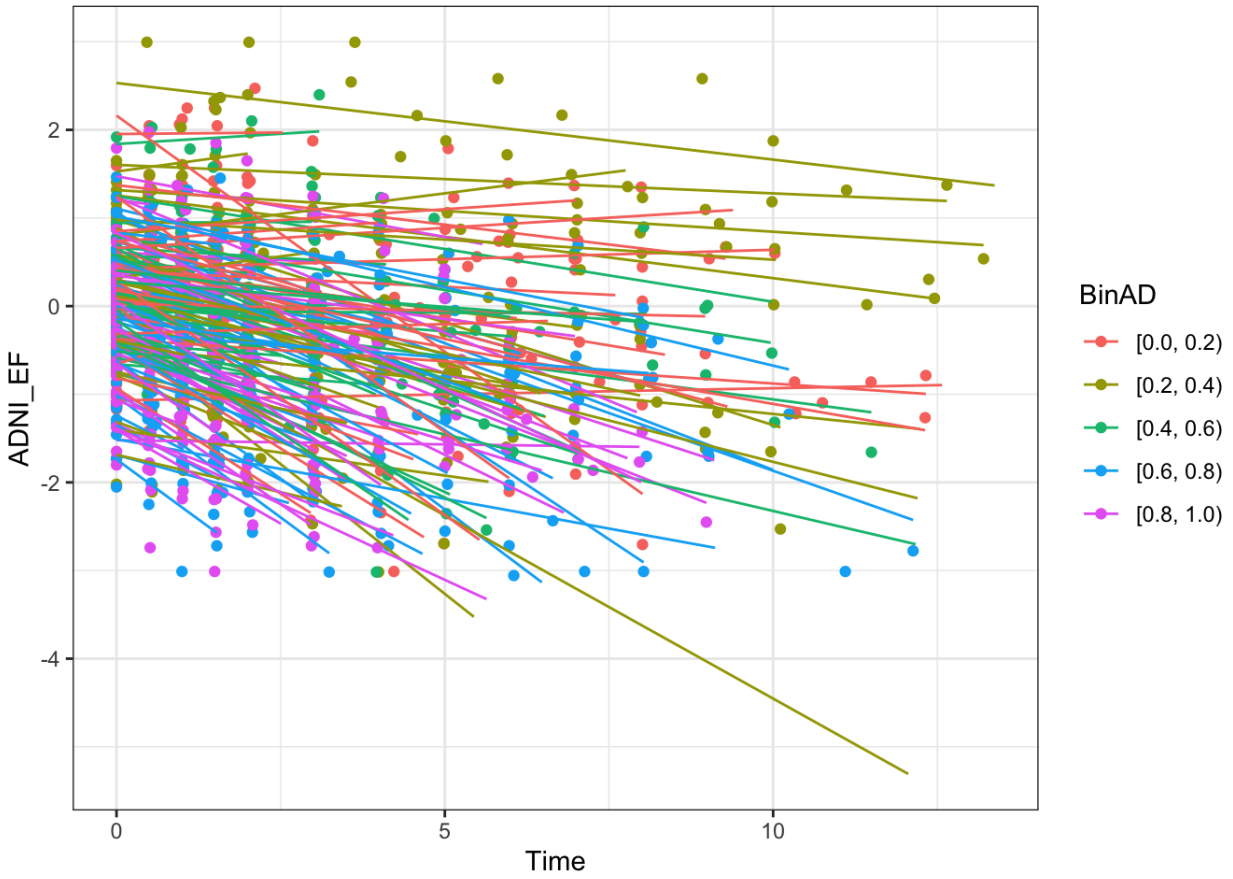
Slope of ADNI-MEM over time (yr)

BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.0, 0.2)	-0.1262188	0.0237849	1911.852	-0.1728660	-0.0795716
[0.2, 0.4)	-0.1871400	0.0240301	1911.852	-0.2342678	-0.1400121
[0.4, 0.6)	-0.1635221	0.0339169	1911.852	-0.2300401	-0.0970042
[0.6, 0.8)	-0.2479559	0.0194972	1911.852	-0.2861939	-0.2097180
[0.8, 1.0)	-0.2758921	0.0215488	1911.852	-0.3181538	-0.2336304

While not perfectly monotonic, there is a trend for ADNI-MEM to worsen faster in the higher P(AD) bins. The sharp contrast is more visible in the plot, where the red (lowest) bin stays about the same or even improves while the blue and magenta (highest) tend to quickly decline

Longitudinal ADNI-EF

```
#LMM_ADNI_EF = fit_longitudinal_GAM(ADNI_EF,longMCIdata)
#saveRDS(LMM_ADNI_EF,file="LMM_ADNI_EF.rdata")
LMM_ADNI_EF = readRDS("LMM_ADNI_EF.rdata")
emm_long_EF = emtrends(LMM_ADNI_EF,pairwise~BinAD,var="Time",adjust="none")
comps_long_EF = as_tibble(emm_long_EF$contrasts) %>% mutate(response="ADNI_EF",type="TimeSlope"
)


set.seed(110)
plot_longitudinal_samples(longMCIdata,LMM_ADNI_EF,35)
```




```
emm_long_EF$emtrends %>% as_tibble() %>% kable(caption="Slope of ADNI-EF over time (yr)")
```

Slope of ADNI-EF over time (yr)

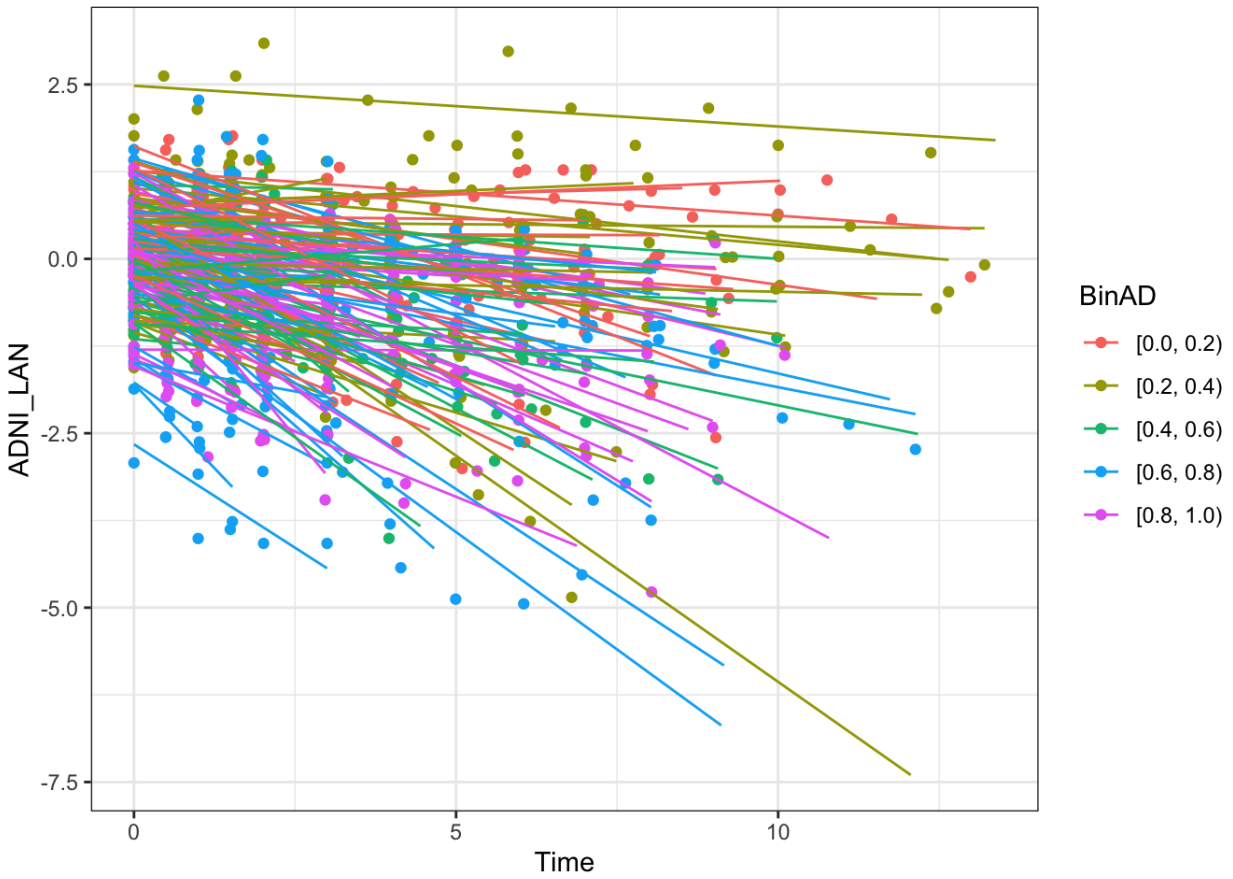
BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.0, 0.2)	-0.0761191	0.0303689	1922.412	-0.1356786	-0.0165597
[0.2, 0.4)	-0.1845026	0.0319662	1922.412	-0.2471946	-0.1218105
[0.4, 0.6)	-0.2192953	0.0425940	1922.412	-0.3028307	-0.1357599

BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.6, 0.8)	-0.3070246	0.0253562	1922.412	-0.3567532	-0.2572960
[0.8, 1.0)	-0.3060882	0.0284985	1922.412	-0.3619796	-0.2501969

As the bin increases, the decrease in executive functioning as assessed by ADNI-EF appears to be amplified, though the change is most aparrant between the lowest (red) and highest groups (blue and magenta)

Longitudinal ADNI-LAN

```
#LMM_ADNI_LAN = fit_longitudinal_GAM(ADNI_LAN,longMCIdata)
#saveRDS(LMM_ADNI_LAN,file="LMM_ADNI_LAN.rdata")
LMM_ADNI_LAN = readRDS("LMM_ADNI_LAN.rdata")
emm_long_LAN = emtrends(LMM_ADNI_LAN,pairwise~BinAD,var="Time",adjust="none")
comps_long_LAN = as_tibble(emm_long_LAN$contrasts) %>% mutate(response="ADNI_LAN",type="TimeSlo
pe")

set.seed(120)
plot_longitudinal_samples(longMCIdata,LMM_ADNI_LAN,35)
```




```
emm_long_LAN$emtrends %>% as_tibble() %>% kable(caption="Slope of ADNI-LAN over time (yr)")
```

Slope of ADNI-LAN over time (yr)

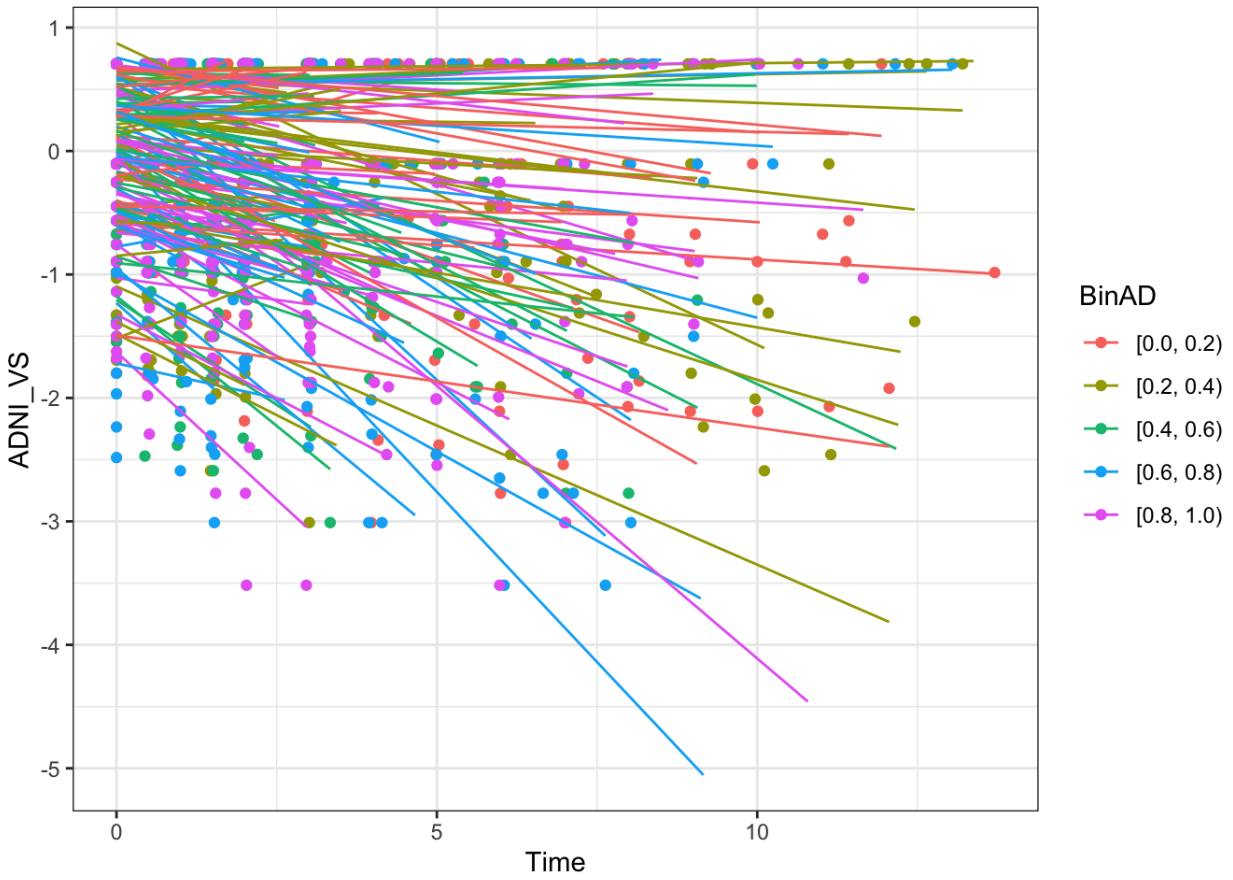
BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.0, 0.2)	-0.1531530	0.0339772	1907.813	-0.2197893	-0.0865167

BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.2, 0.4)	-0.1709967	0.0339721	1907.813	-0.2376230	-0.1043704
[0.4, 0.6)	-0.2006378	0.0490413	1907.813	-0.2968179	-0.1044576
[0.6, 0.8)	-0.3668095	0.0276596	1907.813	-0.4210558	-0.3125632
[0.8, 1.0)	-0.4004843	0.0303339	1907.813	-0.4599754	-0.3409933

Again, the highest bin has a very pronounced downward trend (-0.4 per year) in language assessed by ADNI-LAN. This is also seen in the plot.

Longitudinal ADNI-VS

```
#LMM_ADNI_VS = fit_longitudinal_GAM(ADNI_VS,longMCIdata)
#saveRDS(LMM_ADNI_VS,file="LMM_ADNI_VS.rdata")
LMM_ADNI_VS = readRDS("LMM_ADNI_VS.rdata")
emm_long_VS = emtrends(LMM_ADNI_VS,pairwise~BinAD,var="Time",adjust="none")
comps_long_VS = as_tibble(emm_long_VS$contrasts) %>% mutate(response="ADNI_VS",type="TimeSlope"
)

set.seed(130)
plot_longitudinal_samples(longMCIdata,LMM_ADNI_VS,35)
```




```
emm_long_VS$emtrends %>% as_tibble() %>% kable(caption="Slope of ADNI-VS over time (yr)")
```

Slope of ADNI-VS over time (yr)

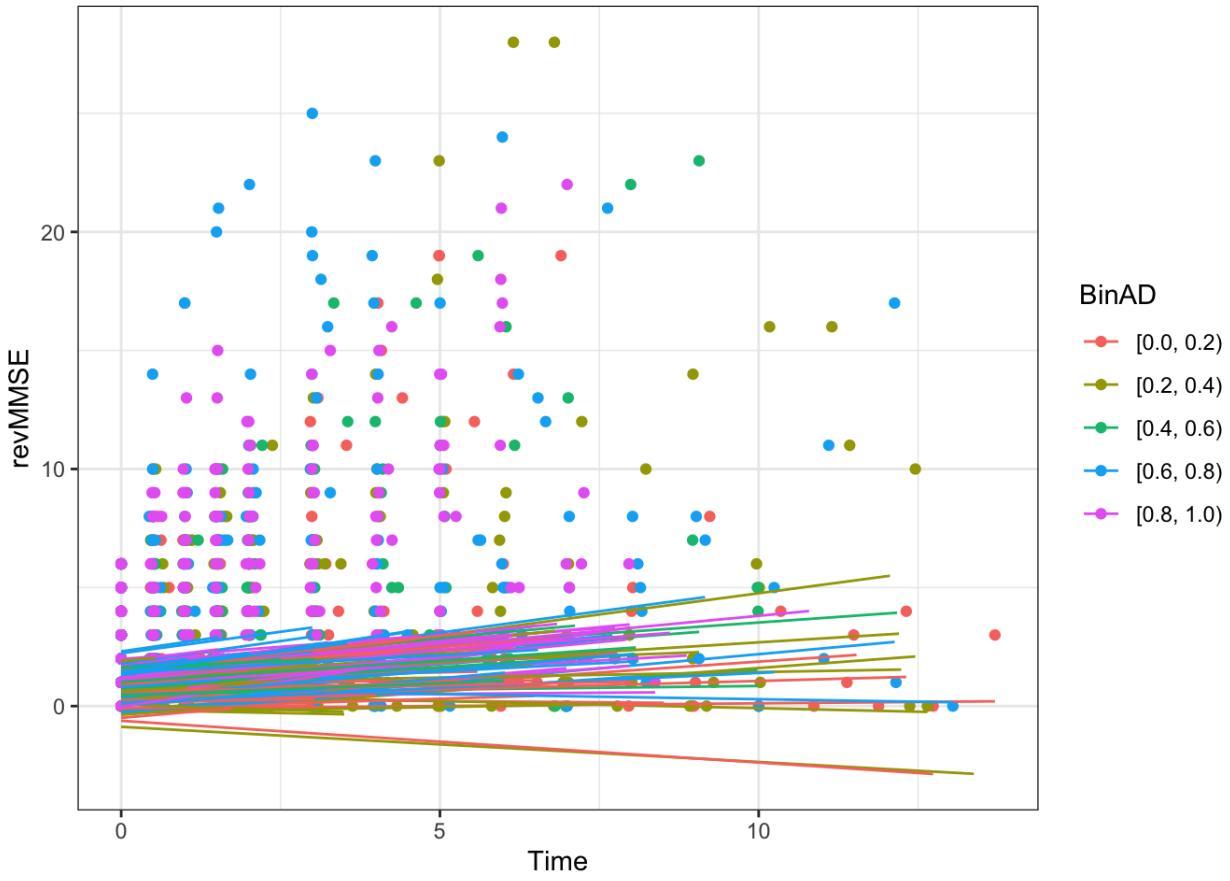
BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.0, 0.2)	-0.0112191	0.0350171	2013.294	-0.0798927	0.0574545
[0.2, 0.4)	-0.0697382	0.0384042	2013.294	-0.1450544	0.0055780
[0.4, 0.6)	-0.1405289	0.0498777	2013.294	-0.2383463	-0.0427115
[0.6, 0.8)	-0.1967620	0.0299378	2013.294	-0.2554743	-0.1380497
[0.8, 1.0)	-0.2457756	0.0335782	2013.294	-0.3116273	-0.1799239

Visuospatial functioning assessed by ADNI-VS also has a faster decline in the higher bin.

Longitudinal MMSE Errors

Recall in this case, higher is worse as this is the change in the number of MMSE errors per year. A negative binomial mixed GAM was used here.

```
#NBGLMM_revMMSE = fit_longitudinal_GAM(revMMSE,longMCIdata,family=nb)
#saveRDS(NBGLMM_revMMSE,file="NBGLMM_revMMSE.rdata")
NBGLMM_revMMSE = readRDS("NBGLMM_revMMSE.rdata")
emm_long_revMMSE = emtrends(NBGLMM_revMMSE,pairwise~BinAD,var="Time",adjust="none")
comps_long_revMMSE = as_tibble(emm_long_revMMSE$contrasts) %>% mutate(response="revMMSE",type=
"TimeSlope")

set.seed(140)
plot_longitudinal_samples(longMCIdata,NBGLMM_revMMSE,35)
```



```
emm_long_revMMSE$emtrends %>% as_tibble() %>% kable(caption="Slope of MMSE Errors over time (y
r)")
```

Slope of MMSE Errors over time (yr)

BinAD	Time.trend	SE	df	lower.CL	upper.CL
[0.0, 0.2)	0.1607801	0.0294640	2031.655	0.1029974	0.2185628
[0.2, 0.4)	0.1579377	0.0282382	2031.655	0.1025588	0.2133166
[0.4, 0.6)	0.2085130	0.0394956	2031.655	0.1310569	0.2859691
[0.6, 0.8)	0.2479026	0.0205047	2031.655	0.2076902	0.2881150
[0.8, 1.0)	0.2681392	0.0228619	2031.655	0.2233039	0.3129744

In this case, the model fit (as a result of the random effects, as well as penalization of the fixed effects in the mixed GAM from mgcv) per patient appears to be highly regularized toward the mean, hence the slopes are somewhat diluted based on the plot.

In the mean results, there is an increase in the error rate with the bin.

Overall FDR Corrected Comparisons

Overall, we have seen that a higher predicted and binned P(AD) based on the lipid and MRI features from Part 1 does seem to correlate with a worsening in cognitive outcome. In this section, we perform more formal contrasts between each bin, for each outcome, and both for baseline and longitudinal. This will involve a Benjamini-Yekutieli (BY) FDR correction for 100 tests. A FDR correction is chosen to instead control the false discovery rate rather than Type I error rate in order to maximize the power, as this is an exploratory data mining analysis. The overall alpha is set to by 0.05.

```
Baseline_Comps = bind_rows(comp_EF,comp_LAN,comp_VS,comp_revMMSE)
Longitudinal_comps = bind_rows(comps_long_MEM,comps_long_EF,comps_long_LAN,comps_long_VS,comps_
long_revMMSE)
all_comps = bind_rows(Baseline_Comps,Longitudinal_comps)
all_comps$pFDR_BY = p.adjust(all_comps$p.value,method="BY")

sig_comps = all_comps %>% filter(pFDR_BY <= 0.05)

kable(sig_comps,caption="Significant Contrasts after BY FDR Correction for 100 tests")
```

Significant Contrasts after BY FDR Correction for 100 tests

contrast	estimate	SE	df	t.ratio	p.value	response	type	pFDR_BY
[0.0, 0.2) - [0.6, 0.8)	-1.2580126	0.3652536	342.3745	-3.444217	0.0006438	revMMSE	Baseline	0.0226544
[0.0, 0.2) - [0.6, 0.8)	0.1217371	0.0307518	1911.8516	3.958694	0.0000781	ADNI_MEM	TimeSlope	0.0035734
[0.0, 0.2) - [0.8, 1.0)	0.1496733	0.0320928	1911.8516	4.663769	0.0000033	ADNI_MEM	TimeSlope	0.0002169
[0.0, 0.2) - [0.6, 0.8)	0.2309055	0.0395596	1922.4123	5.836908	0.0000000	ADNI_EF	TimeSlope	0.0000028
[0.0, 0.2) - [0.8, 1.0)	0.2299691	0.0416431	1922.4123	5.522376	0.0000000	ADNI_EF	TimeSlope	0.0000087
[0.0, 0.2) - [0.6, 0.8)	0.2136565	0.0438060	1907.8128	4.877331	0.0000012	ADNI_LAN	TimeSlope	0.0001065
[0.0, 0.2) - [0.8, 1.0)	0.2473313	0.0455438	1907.8128	5.430624	0.0000001	ADNI_LAN	TimeSlope	0.0000097

contrast	estimate	SE	df	t.ratio	p.value	response	type	pFDR_BY
[0.2, 0.4) - [0.6, 0.8)	0.1958128	0.0438051	1907.8128	4.470091	0.0000083	ADNI_LAN	TimeSlope	0.0004733
[0.2, 0.4) - [0.8, 1.0)	0.2294876	0.0455335	1907.8128	5.039974	0.0000005	ADNI_LAN	TimeSlope	0.0000583
[0.4, 0.6) - [0.8, 1.0)	0.1998466	0.0576630	1907.8128	3.465766	0.0005404	ADNI_LAN	TimeSlope	0.0216898
[0.0, 0.2) - [0.6, 0.8)	0.1855429	0.0460652	2013.2935	4.027834	0.0000584	ADNI_VS	TimeSlope	0.0029673
[0.0, 0.2) - [0.8, 1.0)	0.2345565	0.0485079	2013.2935	4.835432	0.0000014	ADNI_VS	TimeSlope	0.0001090
[0.2, 0.4) - [0.8, 1.0)	0.1760374	0.0510032	2013.2935	3.451495	0.0005690	ADNI_VS	TimeSlope	0.0216898

From the above, we see thatthe MMSE errors (revMMSE=30-MMSE) between the lowest [0,0.2) and second highest [0.6,0.8) bin was the only statistically significant difference at Baseline, with a corrected p value of $p \approx 0.023$.

All other significant contrasts occur in the slopes over time, though none are seen for the MMSE errors (likely due to the regularization dampening the effect above). Within those, it appears that most of the statistically significant differences were seen in ADNI-LAN, indicating that differences in language processing are seen between the probability bins. Many of the statistically significant differences over time occur between the lowest [0,0.2) group and [0.6,0.8) or [0.8,1) group, which was also the difference most clearly visible in the line plots.

Now, the next step is to assess the goodness of fit of each model.

Goodness of Fit (Pseudo Adj R^2)

We can assess goodness of fit to this sample using the pseudo adjusted R^2 metric reported by mgcv gam().

```
get_R2 = function(modelname){
  modelname = enexpr(modelname)
  modelname_char = deparse(modelname)

  modsummary = summary(eval(modelname))
  R2 = modsummary$r.sq
  return(tibble("Model"=modelname_char,"PseudoAdjR2"=R2))
}
```

```
model_names = syms(c("Base_ADNI_EF","Base_ADNI_LAN","Base_ADNI_MEM","Base_ADNI_VS","Base_revMMS
E",
                     "LMM_ADNI_EF","LMM_ADNI_LAN","LMM_ADNI_MEM","LMM_ADNI_VS","NBGLMM_revMMSE"
))

AdjR2_results = map_dfr(model_names,get_R2)

kable(AdjR2_results,caption="Pseudo Adj R2 for each of the models")
```

Pseudo Adj R2 for each of the models

Model	PseudoAdjR2
Base_ADNI_EF	0.1203756
Base_ADNI_LAN	0.1032748
Base_ADNI_MEM	0.0870513

Model	PseudoAdjR2
Base_ADNI_VS	0.0829022
Base_revMMSE	0.0793948
LMM_ADNI_EF	0.8519504
LMM_ADNI_LAN	0.8638107
LMM_ADNI_MEM	0.8953920
LMM_ADNI_VS	0.6181444
NBGLMM_revMMSE	0.8298269

From the above, it is apparent that the baseline models have a very poor fit to the data. This also explains why only the MMSE comparison was significant, as the data may be too noisy at baseline. However, the longitudinal models have a high pseudo adjusted R2 (for what it is worth based on mgcv gam()). This indicates that the fitted mixed GAMs appear to explain the overall patient level trends relatively well, and we can have more faith in the conclusions above.

Conclusion

In summary, in Part 1 we explored different L2 regularized logistic regressions to predict AD from CN as well as the probabilities from a set of lipidomic and MRI volume features. It was found that log transforming these features (and scaling them after) gave the best classification performance. However, the pseudo R2 with this model (and the others) was still low at roughly 0.3-0.4, indicating that the exact probability of AD may be harder to model than classify. Thus we had adopted a binning approach where probabilities were binned in 5 intervals spaced by 0.2 in order to lessen the effects of noise in the exact probabilities. Now, in part 2, we find that there is an overall trend of cognitive outcome worsening over time in the higher P(AD) bins as compared to the lowest. The results from this analysis could be used to identify LMCI patients at risk for developing AD in order to intervene earlier on. It also shows that the signs of AD can appear almost 10-14 years in advance.