Data Preparation

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```
library(tidyverse)
```

```
## Registered S3 methods overwritten by 'ggplot2':
##   method         from
##   [.quosures     rlang
##   c.quosures     rlang
##   print.quosures rlang
```

```
## Registered S3 method overwritten by 'rvest':
##   method            from
##   read_xml.response xml2
```

```
## -- Attaching packages ---------------------------------------------------------------------------
```

```
## v ggplot2 3.1.1       v purrr   0.3.2
## v tibble  2.1.1       v dplyr   0.8.0.1
## v tidyr   0.8.3       v stringr 1.4.0
## v readr   1.3.1       v forcats 0.4.0
```

```
## -- Conflicts ------------------------------------------------------------------------------------ 
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
```

Introduction to Dataset

The Open Access Series of Imaging Studies (OASIS) is a project whose aim is to encourage open analysis of neuroimaging datasets in the scientific community through free distribution and compilation. The OASIS-3 release is a retrospective compilation of longitudinal neuroimaging, clinical, cognitive, and biomarker data of 1098 participants in several research studies at the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University in St. Louis over the course of 30 years. Of included participants, 609 are cognitively normal and 489 are in various stages of cognitive decline, with ages ranging from 42 - 95 years.

First, we'll prepare the data by coding the longitudinal IDs to days and years:

```
freesurfer = read_csv("./data/freesurfer.csv") %>%
  janitor::clean_names() %>%
  select(-fs_date, -included_t1s)
```

```
## Parsed with column specification:
## cols(
##   `FS_FSDATA ID` = col_character(),
##   Session = col_character(),
##   Subject = col_character(),
##   `FS Date` = col_logical(),
##   `Included T1s` = col_logical(),
##   IntraCranialVol = col_double(),
##   lhCortexVol = col_double(),
##   rhCortexVol = col_double(),
```

```
##   CortexVol = col_double(),
##   SubCortGrayVol = col_double(),
##   TotalGrayVol = col_double(),
##   SupraTentorialVol = col_double(),
##   lhCorticalWhiteMatterVol = col_double(),
##   rhCorticalWhiteMatterVol = col_double(),
##   CorticalWhiteMatterVol = col_double()
## )
```

```
clinical_data = read_csv("./data/ClinicalData.csv") %>%
  janitor::clean_names() %>%
  select(-date, -age)
```

```
## Parsed with column specification:
## cols(
##   .default = col_double(),
##   `ADRC_ADRCCLINICALDATA ID` = col_character(),
##   Subject = col_character(),
##   Date = col_logical(),
##   Age = col_logical(),
##   dx1 = col_character(),
##   dx2 = col_character(),
##   dx3 = col_character(),
##   dx4 = col_character(),
##   dx5 = col_character(),
##   acsparnt = col_logical(),
##   primStudy = col_logical(),
##   acsStudy = col_logical()
## )
```

```
## See spec(...) for full column specifications.
```

```
#year preparation
clinical_data <- clinical_data %>%
  mutate(day = str_extract(adrc_adrcclinicaldata_id, "[^_]+$"),
         day = as.numeric(str_remove(day, "d")),
         year = day/365,
         subject = as.numeric(str_remove(subject, "OAS")))

freesurfer <- freesurfer %>%
   mutate(day = str_extract(fs_fsdata_id, "[^_]+$"),
         day = as.numeric(str_remove(day, "d")),
         year = day/365,
         subject = as.numeric(str_remove(subject, "OAS")))
```

Exploratory Data Analysis

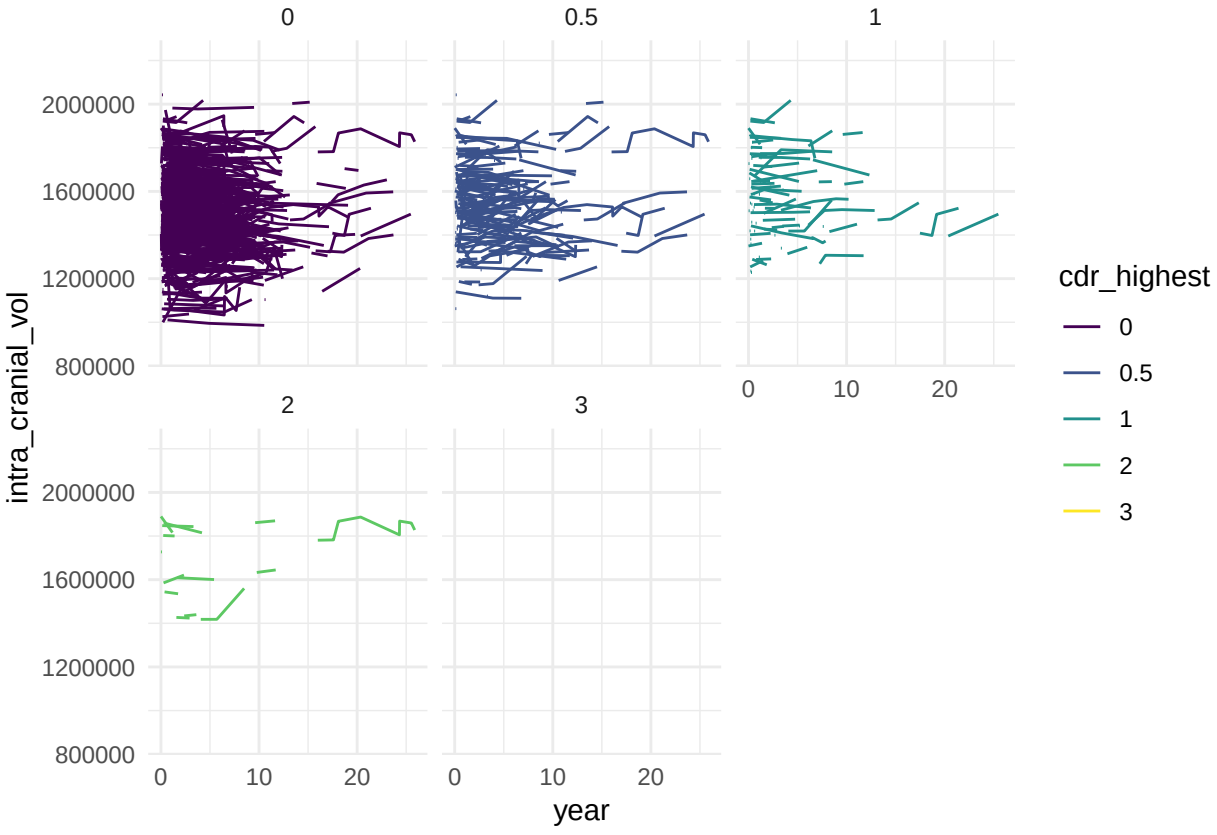
First, we examine the longitudinal structure of the data. What does the Freesurfer-derived MRI data look like over time when patients are classified based on their highest diagnosed CDR (Clinical Dementia Rating) score?

```
#List of highest-ever CDR score
subjects_ever_dementia <- clinical_data %>%
  distinct(subject, cdr, year) %>%
```

```
  mutate(year = glue::glue("year_{round(year)}")) %>%
  rowid_to_column() %>%
  spread(year, cdr)

year_cols <- subjects_ever_dementia %>% select(year_1:year_9) %>% names()

subjects_ever_dementia <- subjects_ever_dementia %>%
  mutate_all(~replace(., is.na(.), 0)) %>%
  mutate(cdr_highest = pmax(!!!rlang::syms(year_cols))) %>%
  mutate(cdr_highest = factor(cdr_highest)) %>%
  select(subject, cdr_highest)
```

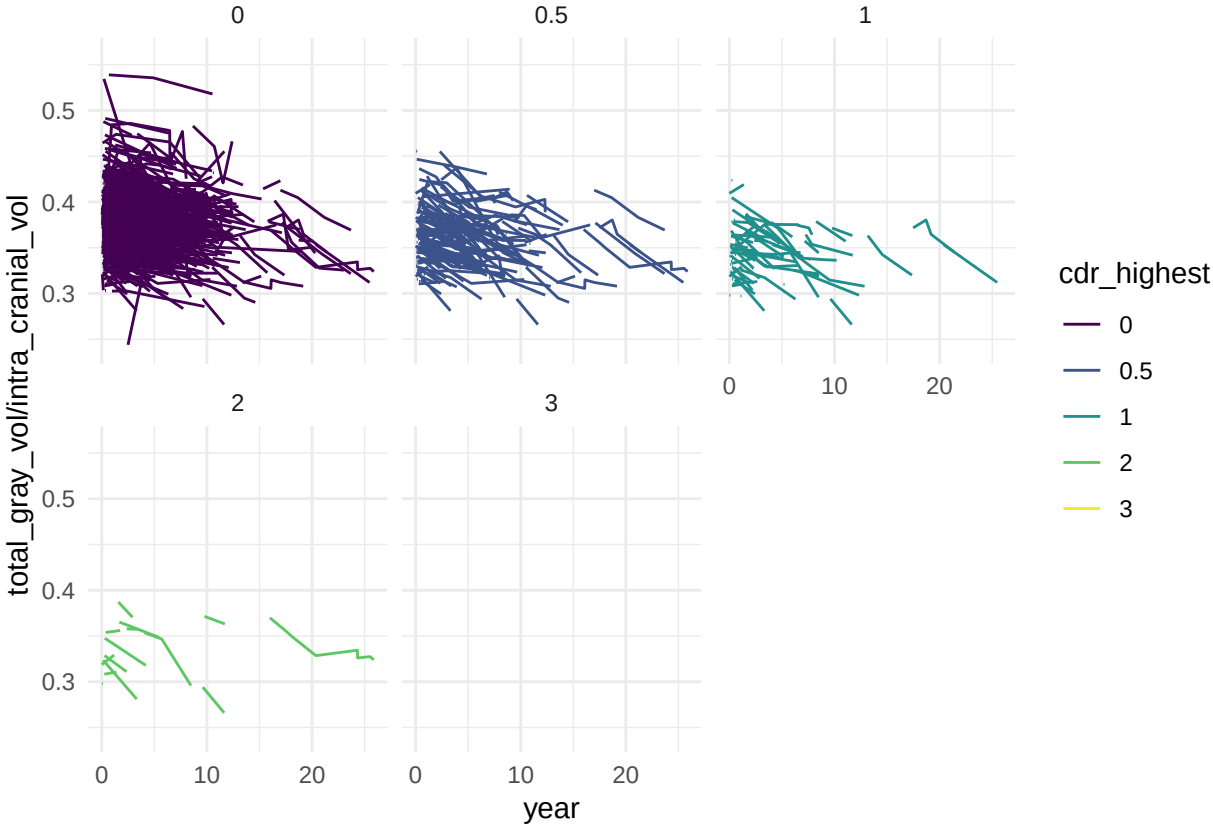
```
#ICV/eTIV
freesurfer %>%
  left_join(subjects_ever_dementia, by = "subject") %>%
  ggplot(aes(y = intra_cranial_vol, x = year, group = subject, color = cdr_highest)) +
  facet_wrap(~cdr_highest, nrow = 2) +
  geom_line() + theme_minimal() + scale_color_viridis_d()
```

```
## geom_path: Each group consists of only one observation. Do you need to
## adjust the group aesthetic?
```



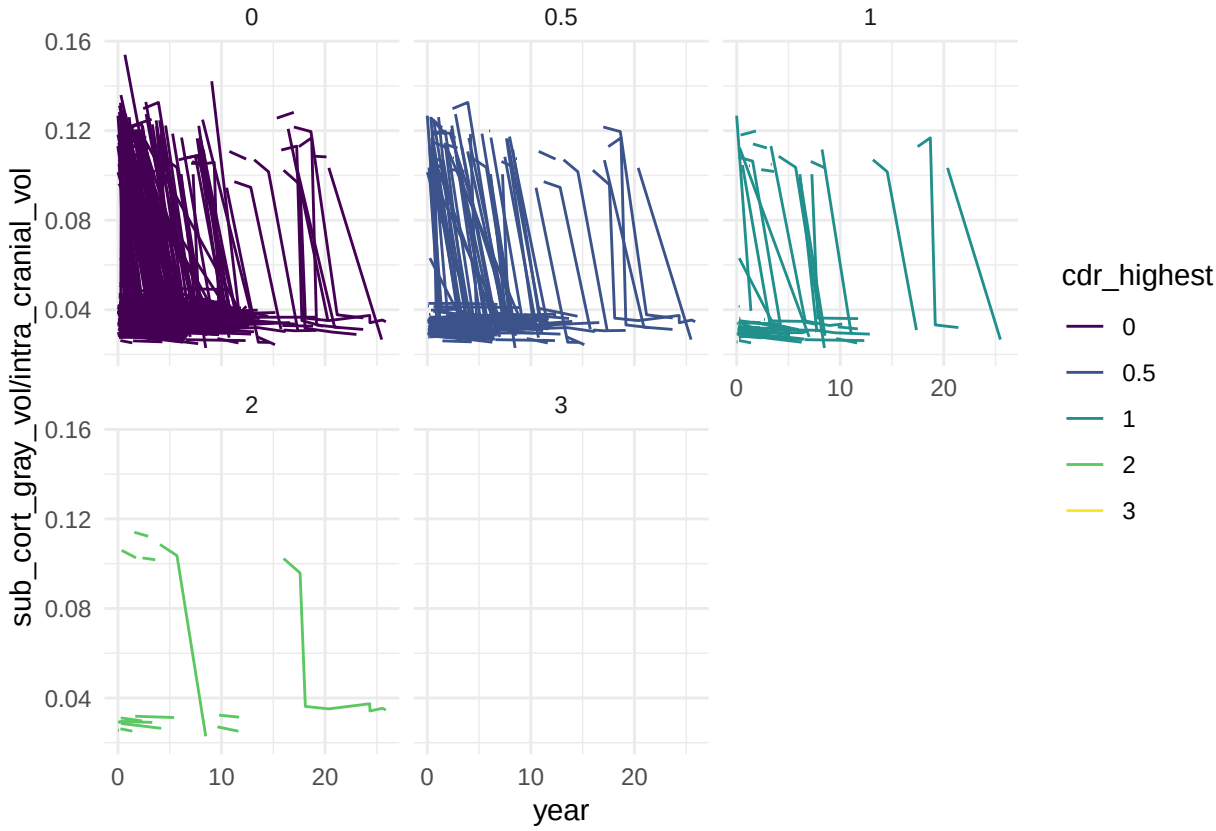

```
#Total gray volume/icv
freesurfer %>%
  left_join(subjects_ever_dementia, by = "subject") %>%
  ggplot(aes(y = total_gray_vol/intra_cranial_vol, x = year, group = subject, color = cdr_highest)) +
  facet_wrap(~cdr_highest, nrow = 2) +
  geom_line() + theme_minimal() + scale_color_viridis_d()
```

```
## geom_path: Each group consists of only one observation. Do you need to
## adjust the group aesthetic?
```



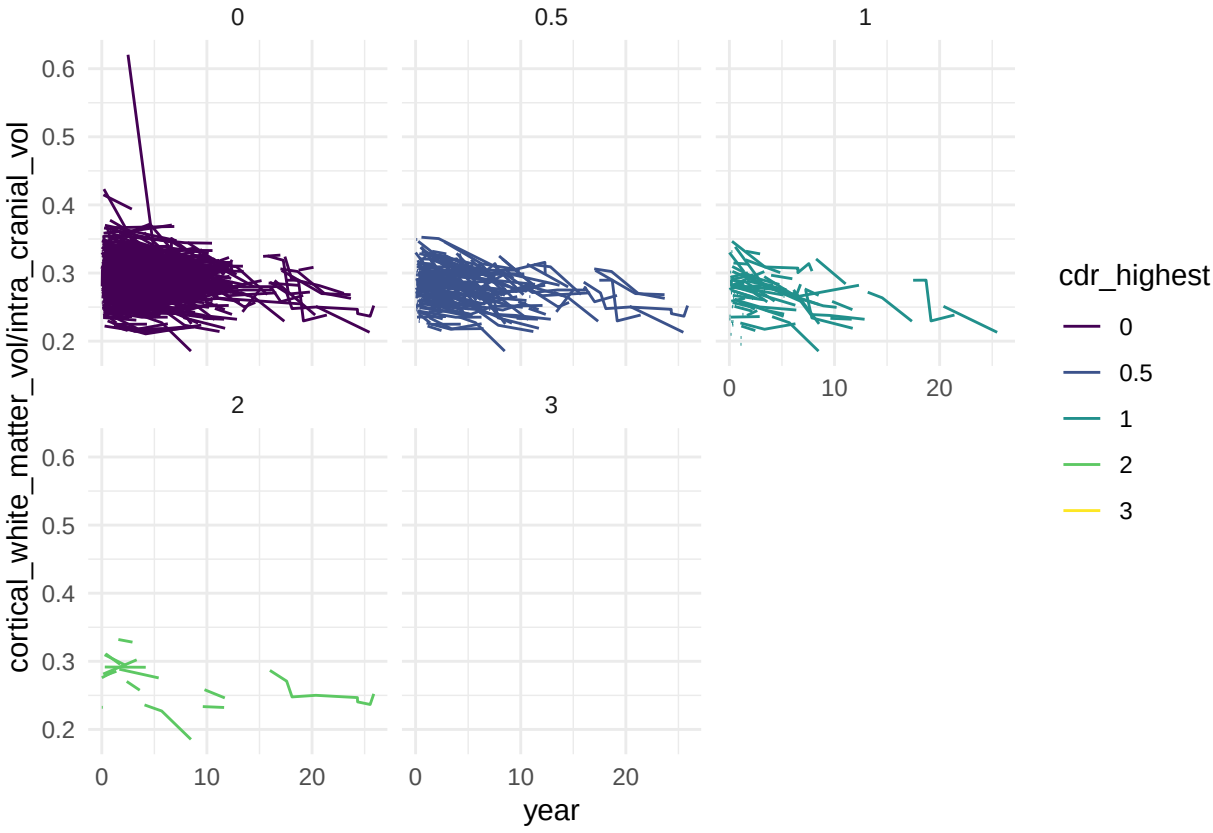

```
#below doesn't look great, maybe b/c of different methods: NOTE: SubCortGray excludes brain stem and ce
freesurfer %>%
  left_join(subjects_ever_dementia, by = "subject") %>%
  ggplot(aes(y = sub_cort_gray_vol/intra_cranial_vol, x = year, group = subject, color = cdr_highest)) +
  facet_wrap(~cdr_highest, nrow = 2) +
  geom_line() + theme_minimal() + scale_color_viridis_d()
```

```
## geom_path: Each group consists of only one observation. Do you need to
## adjust the group aesthetic?
```




```
#total white matter/cv
freesurfer %>%
  left_join(subjects_ever_dementia, by = "subject") %>%
  ggplot(aes(y = cortical_white_matter_vol/intra_cranial_vol, x = year, group = subject, color = cdr_hig
  facet_wrap(~cdr_highest, nrow = 2) +
  geom_line() + theme_minimal() + scale_color_viridis_d()
```

```
## geom_path: Each group consists of only one observation. Do you need to
## adjust the group aesthetic?
```

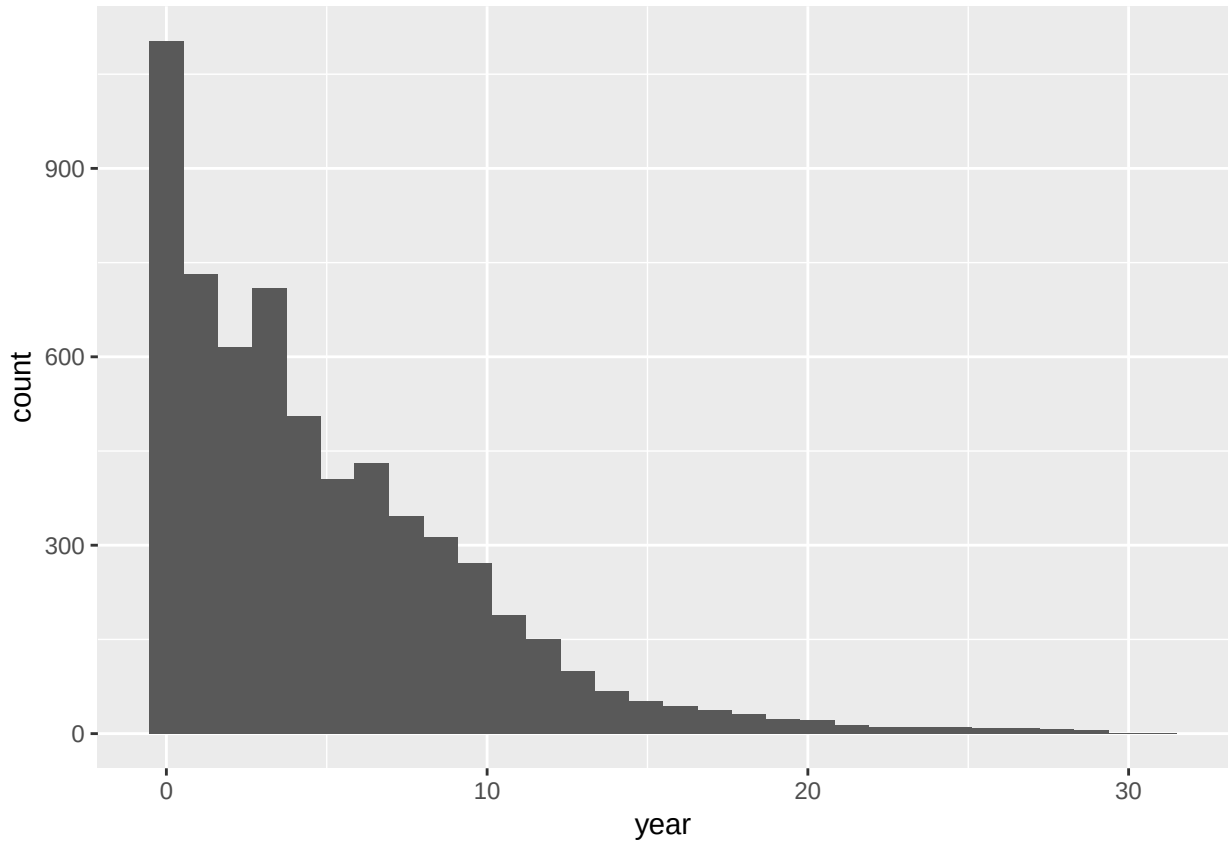


Selecting a time slice

To proceed with our analysis, we'll need to abandon the longitudinal structure of the data. However, we want to preserve as much data as possible while matching anatomical scores to the outcome.

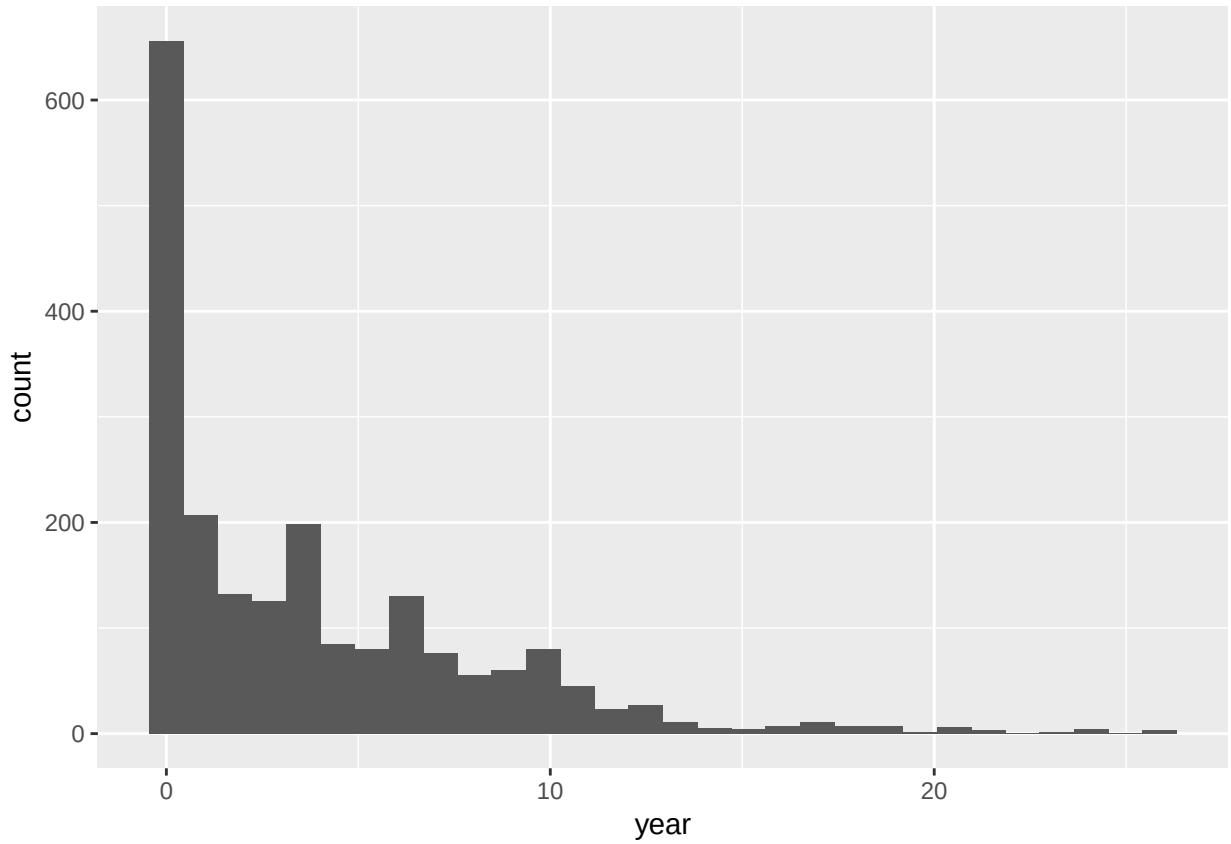
```
clinical_data %>% select(subject, day, year) %>%
  ggplot(aes(x = year)) +
  geom_histogram()
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```




```
freesurfer %>% select(subject, day, year) %>%
  ggplot(aes(x = year)) +
  geom_histogram()
```

```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```




```
#Round to closest year in both datasets
freesurfer <- freesurfer %>%
  mutate(year_round = round(year))

#Merge and remove nonmatched values: effectively matching +- 6 mo.
merged_data <- clinical_data %>%
  mutate(year_round = round(year)) %>%
  left_join(freesurfer, by = c("subject", "year_round")) %>%
  filter(!is.na(adrc_adrcclinicaldata_id), !is.na(fs_fsdata_id)) %>%
  rename(year_clinical = year.x, day_clinical = day.x,
         year_mri = year.y, day_mri = day.y)

#If two entries per year, take the latest one:
merged_data <- merged_data %>%
  group_by(subject, year_round) %>%
  summarize_all(last) %>%
  ungroup()

#Take baseline
baseline_data <- merged_data %>%
  group_by(subject) %>%
  summarize_all(first)

#Take the last measurement
last_data <- merged_data %>%
  group_by(subject) %>%
  summarize_all(last)
```

```
#Take the 2nd measurement
second_data <- merged_data %>%
  group_by(subject) %>%
  summarize_all(~nth(., 2)) %>%
  filter(!is.na(year_round))

#Take the 3nd measurement
third_data <- merged_data %>%
  group_by(subject) %>%
  summarize_all(~nth(., 3)) %>%
  filter(!is.na(year_round))
```

Data preparation

First, we needed to define a rule for matching clinical measurements and MRI data on time. We chose to match based on the closest year, effectively a +- 6 months of difference. When multiple measurements were taken in a single year, we relied on the latest measurement for simplicity.

Although all patients underwent baseline clinical evaluations, some patients only began MRI screens many years into the study. To avoid constraining our sample size to a large extent, after matching the appropriate clinical measurement to the MRI measurements, we did not slice the data on one specific year from baseline; rather, we took the last measurement available for each subject, in the hopes of capturing a more diverse pool of cognitive decline. This leaves us with data from 997 participants, whose clinical and MRI data are matched on time-point.

First, we will dichotomize the outcome into dementia/non dementia by classifying cdr $= 0$ as non-dementia, and cdr > 0 as dementia. We will not consider a multi-class classification model, because of the imbalance of classes:

```
last_data %>%
  mutate(cdr = factor(cdr)) %>%
  count(cdr) %>%
  knitr::kable()
```

cdr	n
0	694
0.5	213
1	82
2	7
3	1

```
cog_data <- last_data %>%
  mutate(cdr = factor(case_when(cdr == 0 ~ 0,
                                cdr > 0 ~ 1),
                      levels = c(0, 1),
                      labels = c("NonDementia", "Dementia"))) %>%
  select(-adrc_adrcclinicaldata_id, -fs_fsdata_id, -starts_with("dx"), -starts_with("day")) %>%
  mutate(age = age_at_entry + year_round) %>%
  select(subject, age, year_round, cdr, mmse, apoe, height, weight, intra_cranial_vol:cortical_white_ma
```

Next, we will code APOE into counts of protective alleles versus risk alleles:

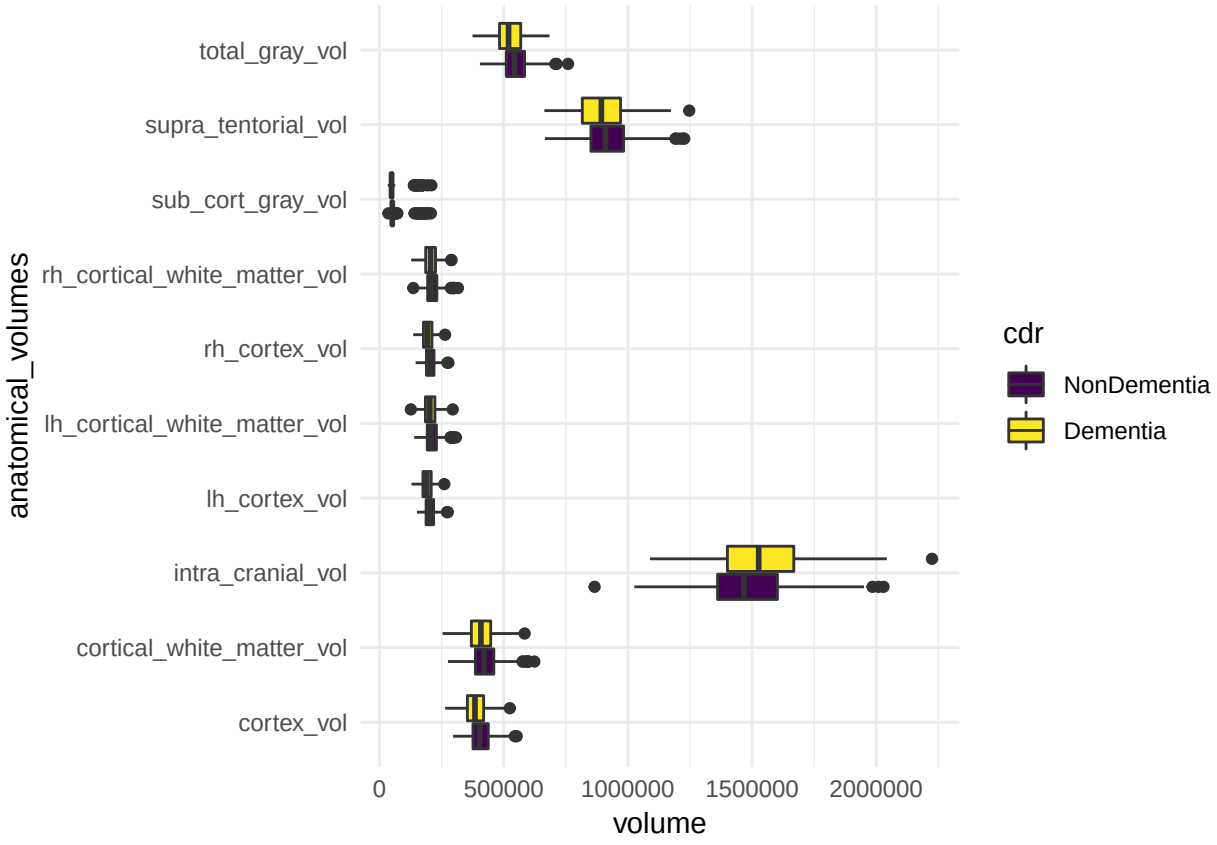
```
#Coding APOE into count of protective allele vs risk allele
cog_data <- cog_data %>%
  mutate(apoe = as.character(apoe)) %>%
  separate(apoe, into = c("apoe_one", "apoe_two"), sep = 1) %>%
  mutate(apoe_one_e2 = if_else(apoe_one == "2", 1, 0),
         apoe_one_e4 = if_else(apoe_one == "4", 1, 0),
         apoe_two_e2 = if_else(apoe_two == "2", 1, 0),
         apoe_two_e4 = if_else(apoe_two == "4", 1, 0)) %>%
  mutate(protective_e2 = apoe_one_e2 + apoe_two_e2,
        risk_e4 = apoe_one_e4 + apoe_two_e4) %>%
  select(subject, year_round, cdr, age, mmse, protective_e2, risk_e4, everything(), -starts_with("apoe")
```

Finally, write our csv:

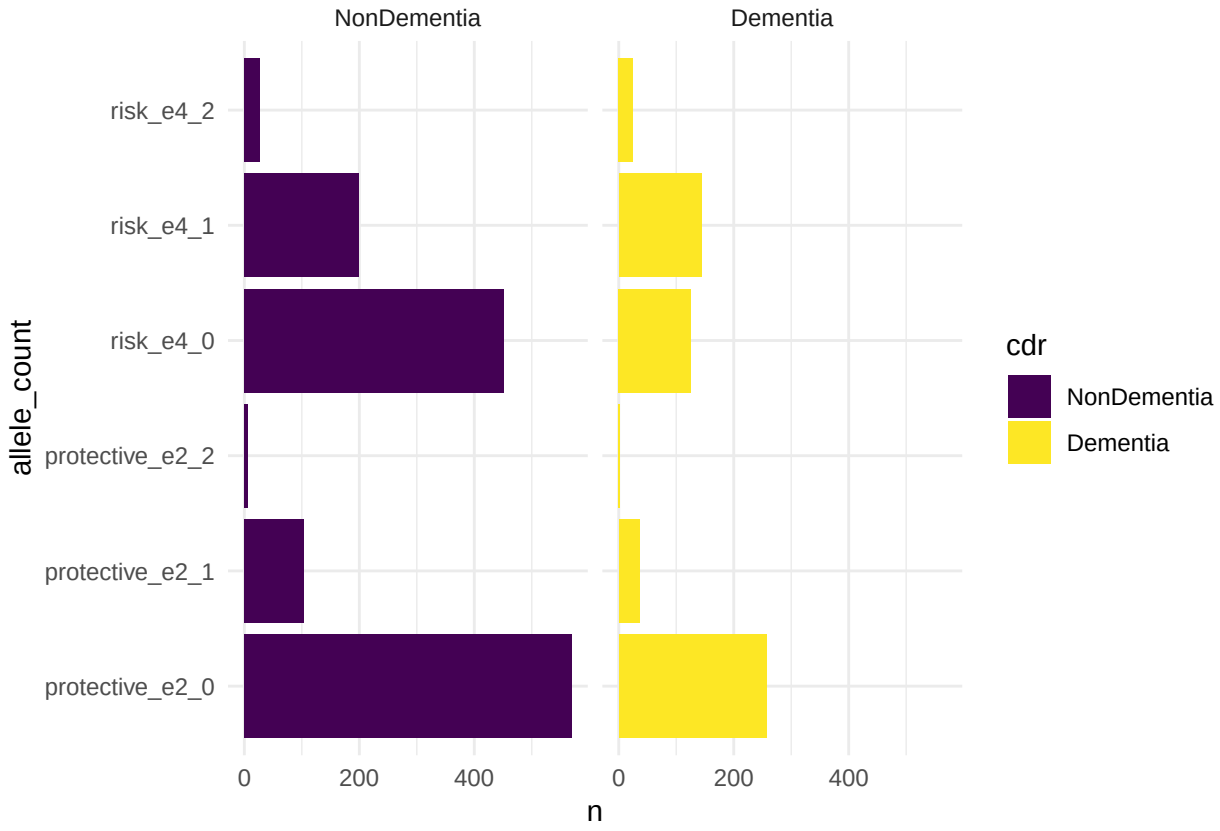
```
write_csv(cog_data, "./data/cog_data")
saveRDS(cog_data, "./data/cog_data.RDS")
```

Plots

```
cog_data %>%
  gather(anatomical_volumes, volume, intra_cranial_vol:cortical_white_matter_vol) %>%
  ggplot(aes(x = anatomical_volumes, y = volume, fill = cdr)) +
  geom_boxplot() +
  coord_flip() +
  theme_minimal() + scale_fill_viridis_d()
```



```
cog_data %>%
  gather(allele, count, protective_e2, risk_e4) %>%
  group_by(cdr, count) %>%
  count(allele) %>%
  drop_na() %>%
  mutate(allele_count = str_c(allele, count, sep = "_")) %>%
  ggplot(aes(x = allele_count, y = n, fill = cdr)) +
  geom_col() +
  coord_flip() +
  facet_grid(~cdr) + scale_fill_viridis_d() + theme_minimal()
```




```
#Relatively equal distributions, slightly more risk alleles in dementia
table(cog_data$cdr, cog_data$protective_e2)
```

```
##
##                  0   1   2
##   NonDementia 569 103   6
##   Dementia    257  36   2
```

```
table(cog_data$cdr, cog_data$risk_e4)
```

```
##
##                  0   1   2
##   NonDementia 451 200  27
##   Dementia    126 144  25
```

From this, it appears that the presence of risk alleles may be more important that the protective alleles as a risk factor for dementia. Further, we note small differences in cortical volumes (aside from total intracranial volume, which is a corrective factor not strictly of interest): white matter volume, cortex volume, and grey

volume seem slightly smaller in the dementia group.

#kmeans

```
library(factoextra) #provides visualization tools for clustering and PCA (ggplot based)
```

```
## Welcome! Related Books: `Practical Guide To Cluster Analysis in R` at https://goo.gl/13EFCZ
```

```
library(gridExtra)
```

```
##
## Attaching package: 'gridExtra'
```

```
## The following object is masked from 'package:dplyr':
##
##     combine
```

```
library(corrplot)
```

```
## corrplot 0.84 loaded
```

```
library(RColorBrewer)  #nice color palettes
library(gplots) #heatmap for better visualization
```

```
##
## Attaching package: 'gplots'
```

```
## The following object is masked from 'package:stats':
##
##     lowess
```

```
library(caret)
```

```
## Loading required package: lattice
```

```
##
## Attaching package: 'caret'
```

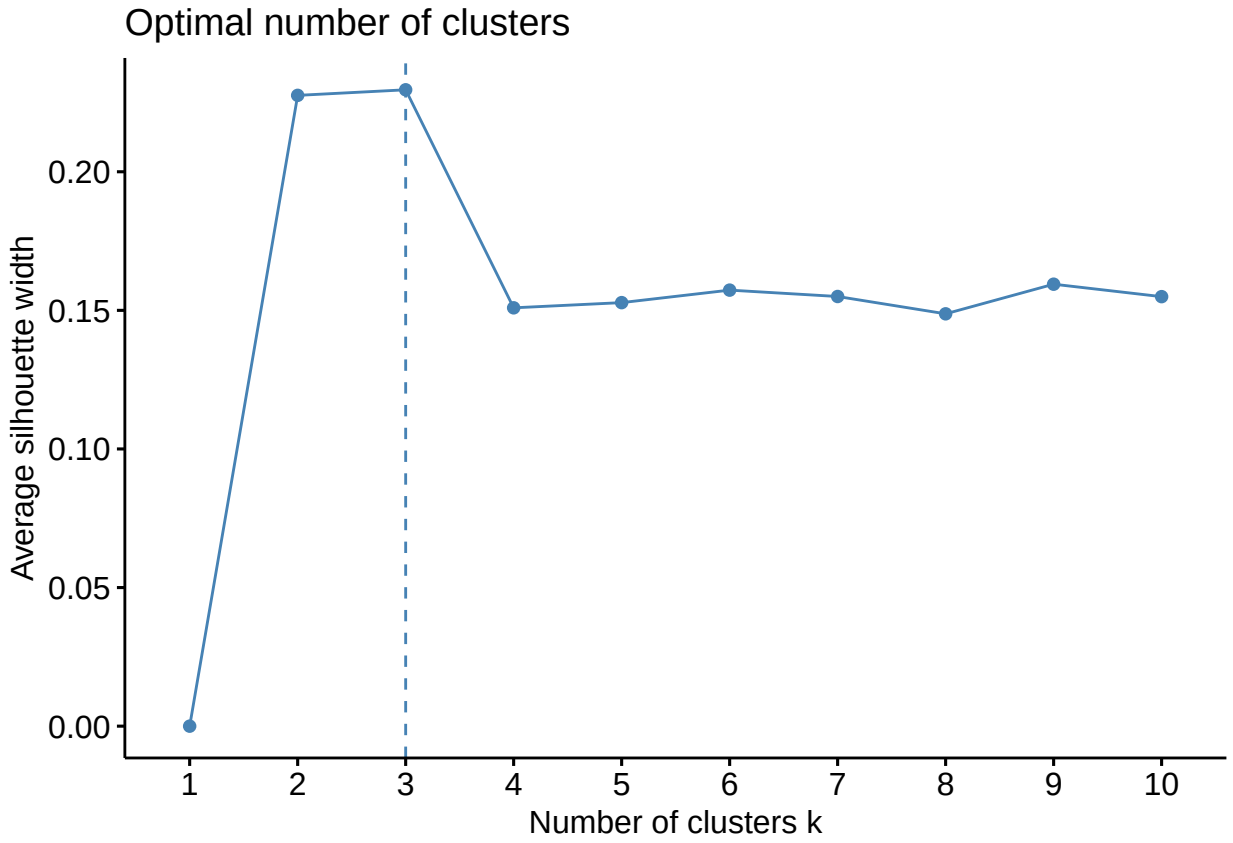
```
## The following object is masked from 'package:purrr':
##
##     lift
```

```
cog_data <- readRDS("./data/cog_data_preproc.RDS")

set.seed(1)
train_index <- createDataPartition(cog_data$cdr, p = 2/3, list = FALSE, times = 1)
cog_train <- cog_data[train_index,]

set.seed(12)
preProc_fn <- preProcess(cog_train[3:10],
           method = c("center", "scale", "knnImpute"),
          k = 5,
          knnSummary = mean,
          verbose = TRUE)
```

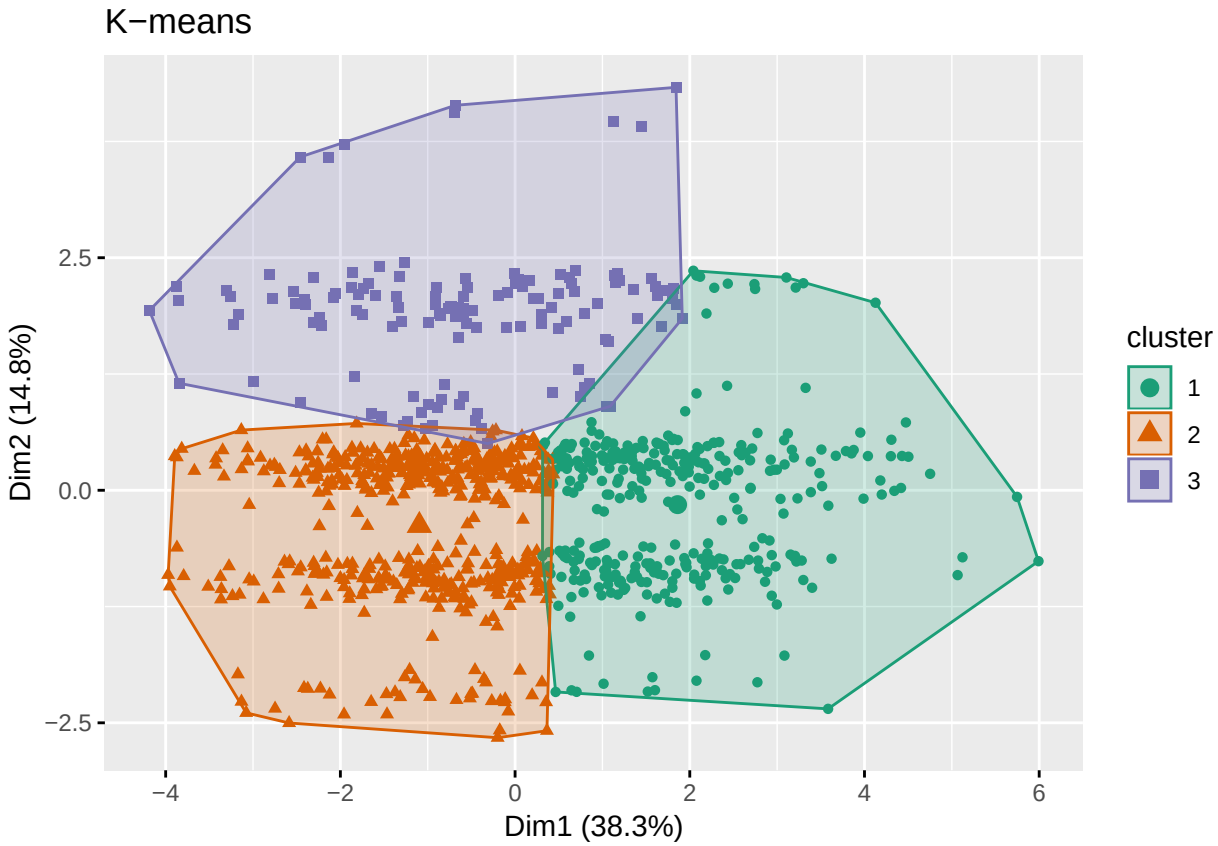
```
## Calculating 8 means for centering
## Calculating 8 standard deviations for scaling
```

```
cog_data[3:10] <- predict(preProc_fn, cog_data[3:10])

# select k through silhouette
```

```r
fviz_nbclust(cog_data[3:10],
             FUNcluster = kmeans,
             method = "silhouette")
```



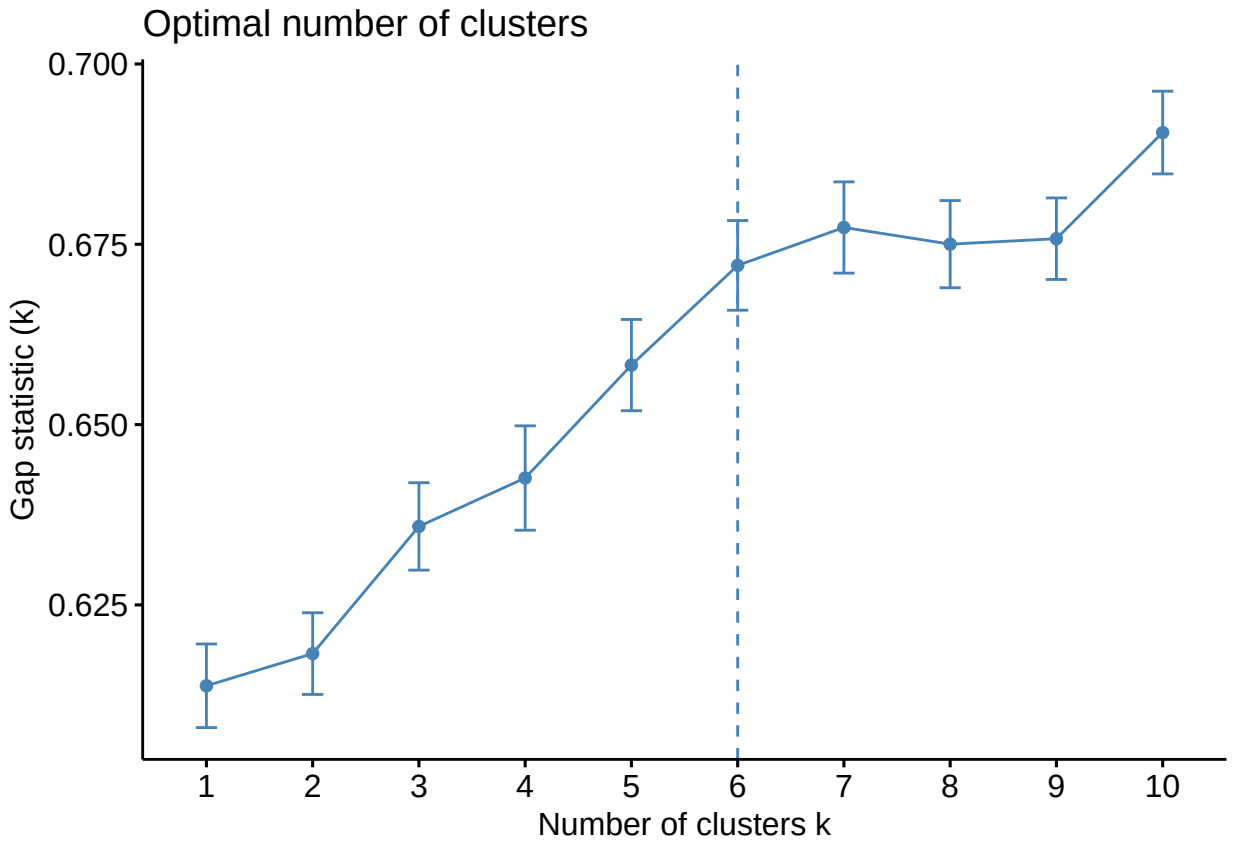

```r
set.seed(1) #because there is randomness in the results
km <- kmeans(cog_data[3:10] , centers = 3, nstart = 20) #because the previous results gave us 3 as the

km_vis <- fviz_cluster(list(data = cog_data[3:10], cluster = km$cluster),
                       ellipse.type = "convex", geom = "point",
                       palette = "Dark2") + labs(title = "K-means")

km_vis
```



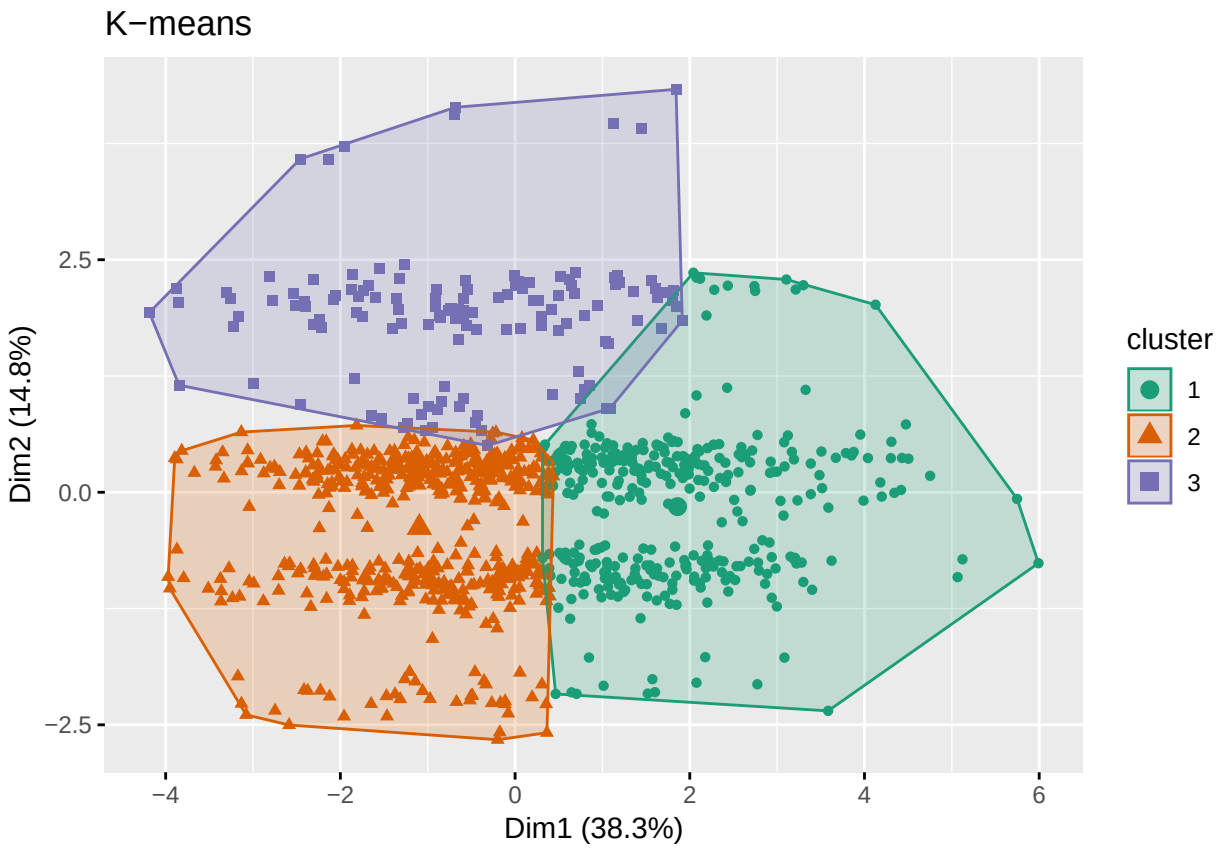

```
cog_data %>%
  mutate(cluster_membership = factor(km$cluster)) %>%
  group_by(cluster_membership) %>%
  count(cdr) %>%
  spread(cdr, n) %>%
  mutate('Cluster Percent Dementia' = Dementia/(NonDementia+ Dementia))
```

```
## # A tibble: 3 x 4
## # Groups:   cluster_membership [3]
##   cluster_membership NonDementia Dementia `Cluster Percent Dementia`
##   <fct>                    <int>    <int>                      <dbl>
## 1 1                          244      105                      0.301
## 2 2                          354      163                      0.315
## 3 3                           96       35                      0.267
```

```
#select k through gap

fviz_nbclust(cog_data[3:10],
             FUNcluster = kmeans,
             method = "gap")
```



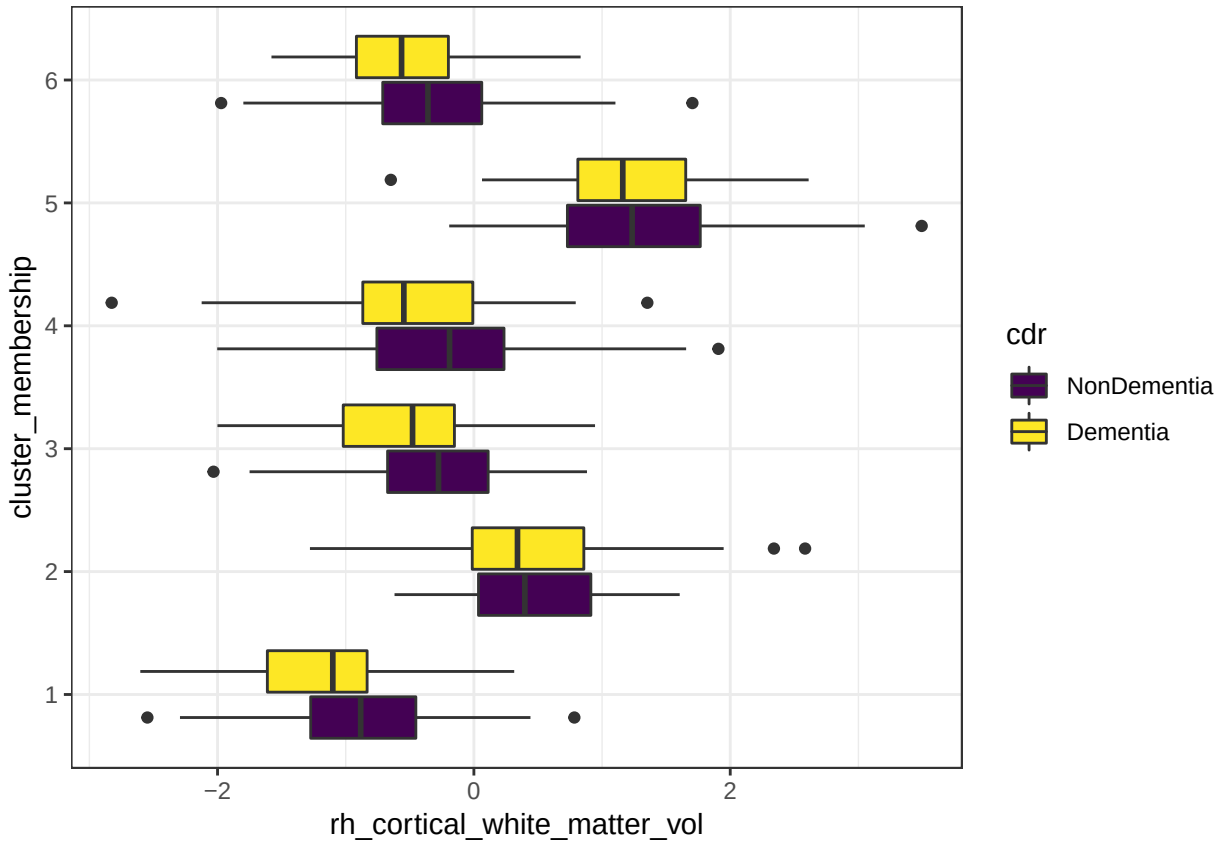

```
set.seed(1) #because there is randomness in the results
km_2 <- kmeans(cog_data[3:10] , centers = 6, nstart = 20)

km_vis <- fviz_cluster(list(data = cog_data[3:10], cluster = km$cluster),
                       ellipse.type = "convex", geom = "point",
                       palette = "Dark2") + labs(title = "K-means")

km_vis
```



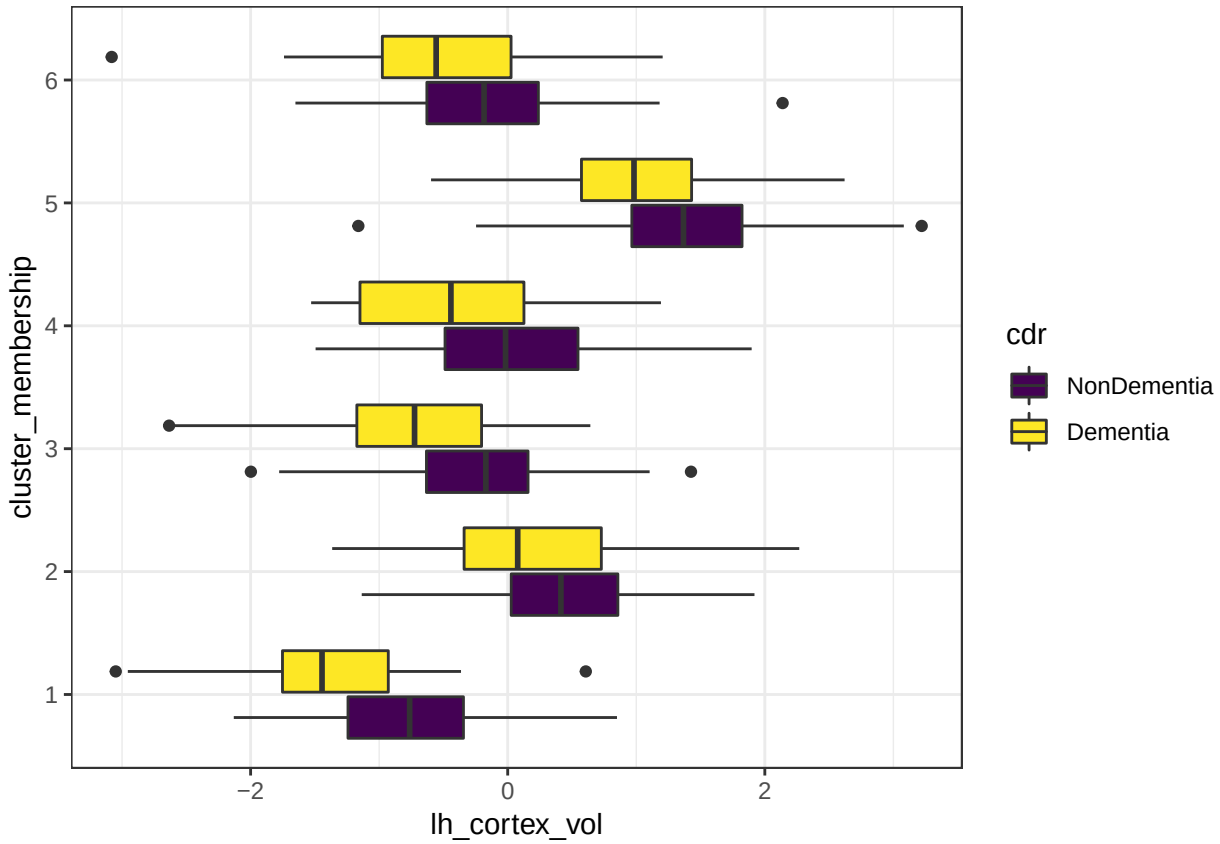

```
cog_data %>%
  mutate(cluster_membership = factor(km_2$cluster)) %>%
  group_by(cluster_membership) %>%
  count(cdr) %>%
  spread(cdr, n) %>%
  mutate('Cluster Percent Dementia' = Dementia/(NonDementia + Dementia))
```

```
## # A tibble: 6 x 4
## # Groups:   cluster_membership [6]
##   cluster_membership NonDementia Dementia `Cluster Percent Dementia`
##   <fct>                    <int>    <int>                      <dbl>
## 1 1                           90       58                      0.392
## 2 2                           99       96                      0.492
## 3 3                          112       67                      0.374
## 4 4                           90       29                      0.244
## 5 5                          128       25                      0.163
## 6 6                          175       28                      0.138
```

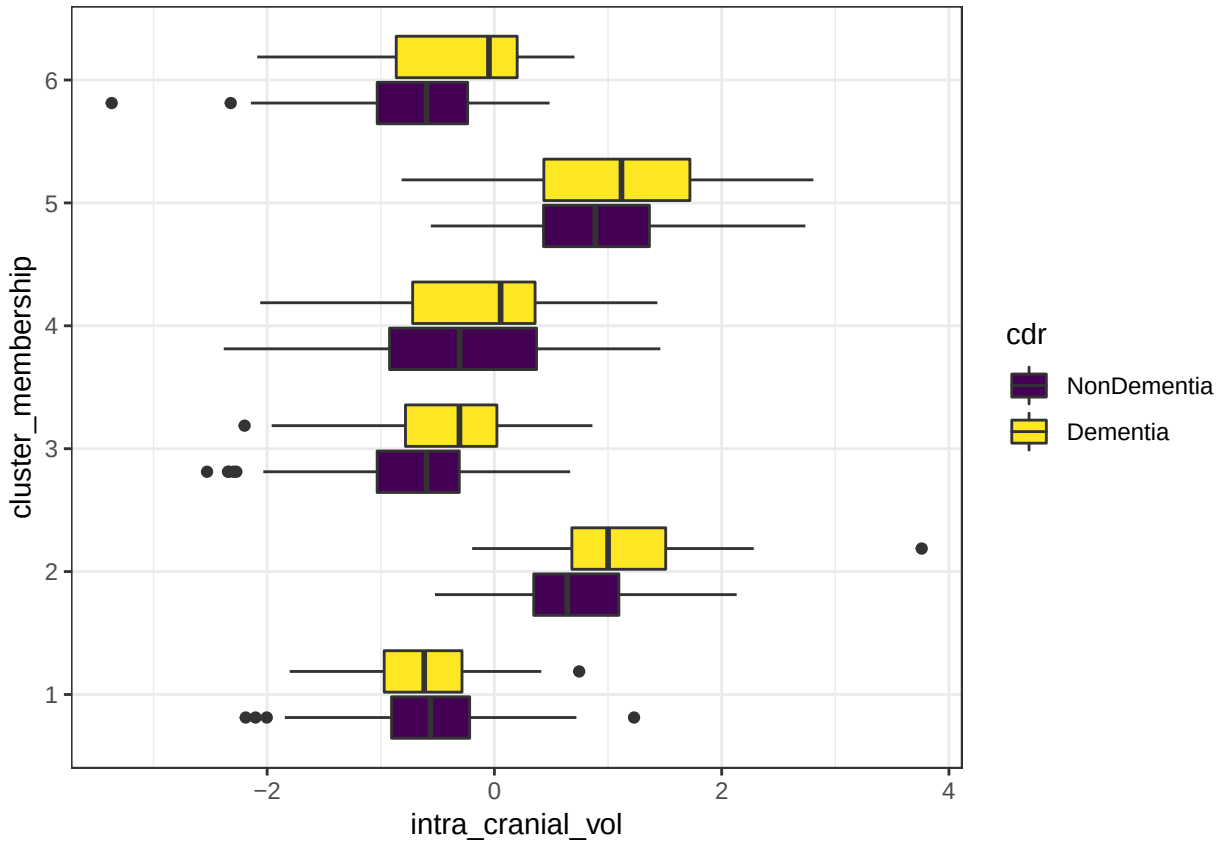
```
#Plots on brain volume show the clustering algorithm found variability not explained by dementia status
cog_data %>%
   mutate(cluster_membership = factor(km_2$cluster)) %>%
  ggplot(aes(y = rh_cortical_white_matter_vol, x = cluster_membership, fill = cdr)) +
  coord_flip() +
  geom_boxplot() + theme_bw() + scale_fill_viridis_d()
```



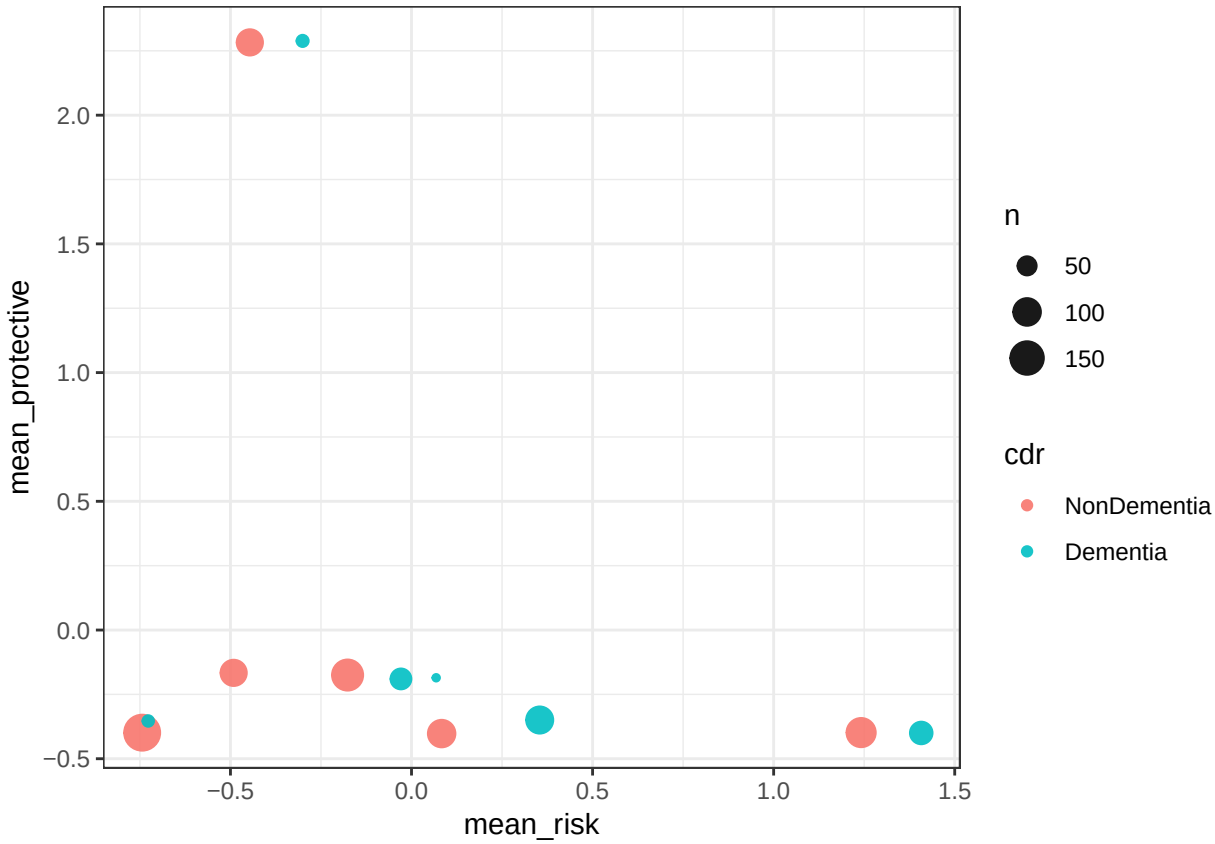

```
cog_data %>%
   mutate(cluster_membership = factor(km_2$cluster)) %>%
  ggplot(aes(y = lh_cortex_vol, x = cluster_membership, fill = cdr)) +
  coord_flip() +
  geom_boxplot() + theme_bw() + scale_fill_viridis_d()
```




```
cog_data %>%
   mutate(cluster_membership = factor(km_2$cluster)) %>%
  ggplot(aes(y = intra_cranial_vol, x = cluster_membership, fill = cdr)) +
  coord_flip() +
  geom_boxplot() + theme_bw() + scale_fill_viridis_d()
```




```
#not terribly useful plot of cluster means of standardized counts of e2/e4 alleles  by dementia status
cog_data %>%
   mutate(cluster_membership = factor(km_2$cluster)) %>%
  group_by(cluster_membership, cdr) %>%
  count(mean_risk = mean(risk_e4), mean_protective = mean(protective_e2)) %>%
  ggplot(aes(x = mean_risk, y = mean_protective, size = n, color = cdr)) +
  geom_point(alpha = 0.9) + theme_bw()
```


mean_protective
2.0
1.5
1.0
0.5
0.0
−0.5
−0.5
0.0
0.5
1.0
1.5
mean_risk
n
50
100
150
cdr
NonDementia
Dementia