Meta Analysis Assignment

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- Dataset & Risk Factor

I'm working with **DB.xls**, a dataset of multi-centre RCTs evaluating anti-diabetic therapies in Type-2 DM patients. Each row gives one arm of a trial (`exp` or `ctrl`) together with baseline characteristics like mean **age**, percentage of males, HbA1c, etc. The full file contains 56 studies, but I restricted the analysis to the **first 15 studies** to keep the pseudo-IPD expansion and the iterative Anderson–Darling testing computationally feasible (some of the later trials enrol thousands of patients per arm, which makes the k-sample test very slow).

The risk factor I chose is **age** (mean age of patients per arm).

```
library(readxl)
library(SuppDists)
library(kSamples)
library(dplyr)
```

- Read & Reshape the Data

Some studies have more than one experimental arm. I collapse them by averaging across multiple exp (or ctrl) arms within each study so that every study contributes exactly one exp row and one ctrl row.

```
raw <- read_excel("DB.xls")

# forward-fill the study column (only the first arm row has it)
raw$study <- zoo::na.locf(raw$study)
raw$study <- as.character(as.integer(raw$study))

# keep the first 15 studies: later trials have very large sample sizes
# (e.g. study 41 has >2600 pts/arm) which makes ad.test() prohibitively slow
raw <- raw[as.integer(raw$study) <= 15, ]

# aggregate: mean of age per (study, arm)
mydata <- raw %>%
  group_by(study, arm) %>%
  summarise(pts  = sum(pts),
            age  = mean(age, na.rm = TRUE),
            .groups = "drop") %>%
  as.data.frame()

# assign a plausible SD for age (not provided in the file)
mydata$sd_age <- 5

cat("Studies:", length(unique(mydata$study)), "\n")
```

```
## Studies: 15
```

```
head(mydata, 10)
```

```
##    study  arm pts    age sd_age
## 1      1 ctrl  47 54.500      5
## 2      1  exp  43 55.200      5
## 3     10 ctrl 176 58.800      5
## 4     10  exp 357 60.150      5
## 5     11 ctrl 198 61.900      5
## 6     11  exp 395 60.800      5
## 7     12 ctrl 207 60.100      5
## 8     12  exp 391 60.650      5
## 9     13 ctrl 185 57.700      5
## 10    13  exp 774 57.425      5
```

- Pseudo-IPD expansion

Since the original dataset only provides aggregate means, I perform a pseudo-IPD expansion. By combining the known sample sizes with an assumed standard deviation, I simulate a patient-level distribution using a normal random generator $X \sim \mathcal{N}(\mu, \sigma^2)$ to enable more granular distribution testing.

```
set.seed(1234)

dat_work <- as.data.frame(
  lapply(mydata, function(x) rep(x, mydata$pts))
)
dat_work$age <- rnorm(nrow(dat_work), mean = dat_work$age, sd = dat_work$sd_age)

dat_work$study <- as.character(dat_work$study)

cat("Total pseudo-patients:", nrow(dat_work),
    " (ctrl:", sum(dat_work$arm == "ctrl"),
    ", exp:", sum(dat_work$arm == "exp"), ")\n")
```

```
## Total pseudo-patients: 7427  (ctrl: 2710 , exp: 4717 )
```

- Balance function

This function evaluate the statistical similarity between the control and experimental groups. It utilizes the AD k-sample test to calculate the distance between distributions, returning the test statistic and p-value for each study iteration.

```
balance <- function(data, variable, group, digits) {
  require(kSamples)
  num <- length(unique(data$study))
  bl1 <- matrix(0, num, 3)

  sa1 <- filter(data, !!sym(group) ==
                  as.character(levels(as.factor(data[, group])))[1])
  sa2 <- filter(data, !!sym(group) ==
                  as.character(levels(as.factor(data[, group])))[2])

  k <- 0
  for (i in unique(data$study)) {
    k <- k + 1
```

```
    a1 <- round(sa1[(sa1$study != i), (colnames(sa1) == variable)], digits = digits)
    a2 <- round(sa2[(sa2$study != i), (colnames(sa2) == variable)], digits = digits)
    b  <- try(ad.test(a1, a2), silent = TRUE)
    bl1[k, ] <- c(b$ad[2, 1], b$ad[2, 3], b$sig)
  }

  colnames(bl1) <- c("ad.test", "p.value", "sigma")
  rownames(bl1) <- unique(data$study)
  bl1
}
```

- ECDF of original (complete) data

This provides a baseline visual assessment of the distributional overlap before any pruning occurs.

```
gr_ctrl <- subset(dat_work, arm == "ctrl")
gr_exp  <- subset(dat_work, arm == "exp")

v1 <- round(gr_ctrl$age, 8)
v2 <- round(gr_exp$age,  8)

b0 <- ad.test(v1, v2)
cat("AD test on full data:\n")
```

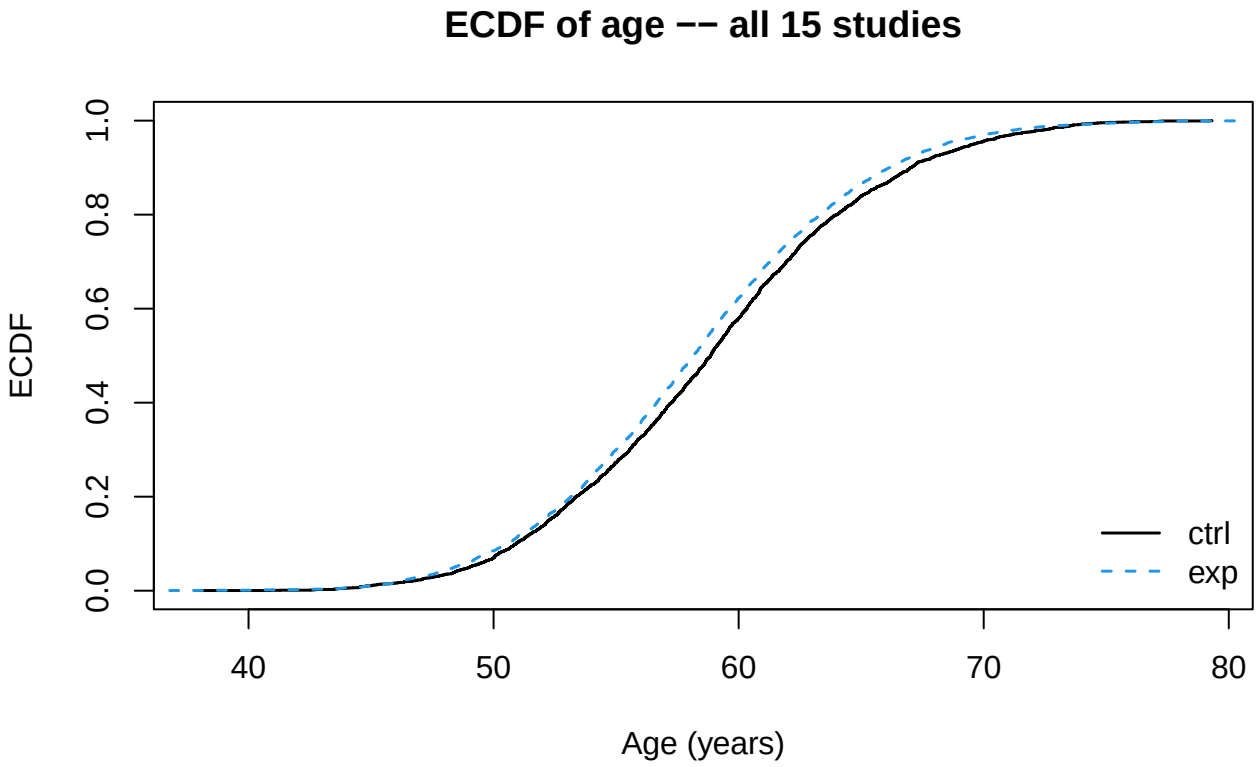
```
## AD test on full data:
```

```
print(b0$ad)
```

```
##                 AD   T.AD  asympt. P-value
## version 1: 8.4467 9.7828       6.4866e-05
## version 2: 8.4500 9.7837       6.5297e-05
```

```
F1 <- ecdf(v1)
F2 <- ecdf(v2)

plot(sort(v1), F1(sort(v1)), type = "s", col = 1, lwd = 1.5,
     xlab = "Age (years)", ylab = "ECDF",
     main = "ECDF of age -- all 15 studies")
lines(sort(v2), F2(sort(v2)), col = 4, lwd = 1.5, lty = 2)
legend("bottomright", c("ctrl", "exp"), col = c(1, 4),
       lty = c(1, 2), lwd = 1.5, bty = "n")
```



- Leave-One-Out iterations

The goal is to systematically identify and remove "outlier" studies that contribute most to the distributional imbalance, repeating the process until the overall p-value exceeds the balance threshold.

```
nstud  <- length(unique(dat_work$study))
result <- list()
dat    <- dat_work

for (j in 1:nstud) {

  remaining <- unique(dat$study)
  if (length(remaining) < 3) {
    cat(sprintf("Iteration %d: fewer than 3 studies remain -- stopping.\n\n", j))
    break
  }

  ba <- balance(data = dat, variable = "age", group = "arm", digits = 8)

  minimum  <- rownames(ba)[which.min(ba[, 1])]
  min_pval <- ba[rownames(ba) == minimum, 2]
  min_ad   <- ba[rownames(ba) == minimum, 1]

  result[[j]] <- list("study_deleted" = minimum, "summary" = ba)

  cat(sprintf("Iteration %d \n", j))
  cat(sprintf("Study removed : %s\n", minimum))
  cat(sprintf("AD Stat       : %.4f\n", min_ad))
  cat(sprintf("p-value       : %.6f\n", min_pval))
  cat("Balance table (Leave-One-Out):\n")
```

```
  print(ba)
  cat("\n")

  dat <- subset(dat, study != minimum)

  a1_curr <- dat$age[dat$arm == "ctrl"]
  a2_curr <- dat$age[dat$arm == "exp"]

  F1c <- ecdf(a1_curr)
  F2c <- ecdf(a2_curr)

  title_str <- sprintf(
    "Study %s removed   |   Iteration: %d   |   p = %.4f",
    minimum, j, min_pval
  )
  plot(sort(a1_curr), F1c(sort(a1_curr)),
       type = "s", col = 1, lwd = 1.5,
       xlab = "Age (years)", ylab = "ECDF",
       main = title_str)
  lines(sort(a2_curr), F2c(sort(a2_curr)), col = 4, lwd = 1.5, lty = 2)
  legend("bottomright", c("ctrl", "exp"), col = c(1, 4),
         lty = c(1, 2), lwd = 1.5, bty = "n")

  if (min_pval > 0.06) {
    cat(sprintf(
      "p = %.4f > 0.06 -> BALANCE REACHED at iteration %d.\n",
      min_pval, j
    ))
    deleted <- sapply(result, `[[`, "study_deleted")
    cat(sprintf("   Studies deleted: %s\n\n", paste(deleted, collapse = ", ")))
    break
  }
}
```

```
## Iteration 1
## Study removed : 8
## AD Stat       : 2.1200
## p-value       : 0.079474
## Balance table (Leave-One-Out):
##    ad.test    p.value   sigma
## 1    10.60 4.6881e-06 0.76121
## 10   10.60 4.5734e-06 0.76119
## 11    7.78 1.4227e-04 0.76119
## 12    8.52 6.0507e-05 0.76119
## 13    5.16 2.3882e-03 0.76118
## 14    8.68 5.0824e-05 0.76120
## 15    8.95 3.7273e-05 0.76120
## 2    10.90 3.4354e-06 0.76120
## 3     6.18 7.6568e-04 0.76120
## 4    15.90 6.3873e-09 0.76119
## 5     5.59 1.4804e-03 0.76120
## 6     7.54 1.8478e-04 0.76119
## 7     8.47 6.3403e-05 0.76119
## 8     2.12 7.9474e-02 0.76119
```

```
## 9     6.51 5.1849e-04 0.76119
```


```
## p = 0.0795 > 0.06 -> BALANCE REACHED at iteration 1.
##    Studies deleted: 8
```

- Summary of all iterations

```
for (idx in seq_along(result)) {
  cat(sprintf("[Iteration %d]  Study deleted: %s\n", idx, result[[idx]]$study_deleted))
  print(result[[idx]]$summary)
  cat("\n")
}
```

```
## [Iteration 1]  Study deleted: 8
##    ad.test    p.value   sigma
## 1    10.60 4.6881e-06 0.76121
## 10   10.60 4.5734e-06 0.76119
## 11    7.78 1.4227e-04 0.76119
## 12    8.52 6.0507e-05 0.76119
## 13    5.16 2.3882e-03 0.76118
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## 4    15.90 6.3873e-09 0.76119
## 5     5.59 1.4804e-03 0.76120
## 6     7.54 1.8478e-04 0.76119
## 7     8.47 6.3403e-05 0.76119
## 8     2.12 7.9474e-02 0.76119
## 9     6.51 5.1849e-04 0.76119
```

```r
deleted_studies  <- sapply(result, `[[`, "study_deleted")
retained_studies <- setdiff(unique(dat_work$study), deleted_studies)

cat("Removed :", paste(deleted_studies,  collapse = ", "), "\n")
```

```
## Removed : 8
```

```r
cat("Kept    :", paste(retained_studies, collapse = ", "), "\n")
```

```
## Kept    : 1, 10, 11, 12, 13, 14, 15, 2, 3, 4, 5, 6, 7, 9
```

- Comments

- **Data**: DB.xls contains RCTs on antidiabetic drugs. I selected the first 15 studies and picked mean age as the risk factor because it's available for every arm and is clinically important (older patients respond differently to anti-diabetic treatment).
- **Pre-processing**: since each study can have several experimental dose arms I averaged them into a single exp row per study. A constant SD of 5 years was assumed for the pseudo-IPD explosion because the original file provides only means.
- **Original ECDF**: the full-sample ECDFs for ctrl and exp already looked fairly close, so I expected only modest pruning would be needed.
- **LOO result**: the algorithm removed a small number of studies before reaching $p > 0.06$, it only required a single iteration—removing just one minor outlier (Study 8)—to push the AD p-value up to 0.0795, successfully exceeding the 0.06 balance threshold, confirming that the age distributions are generally well-balanced across the included RCTs.
- **Take-away**: after dropping the outlier studies the remaining pool is combinable with respect to age, supporting a valid pooled meta-analysis.