

# **Comparative Effectiveness and Personalized Medicine Research Using Real-World Data**

Thomas P. A. Debray, Tri-Long Nguyen, and Robert W. Platt

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# 1 Preface

Thomas Debray (Smart Data Analysis and Statistics B.V.)

This book provides practical guidance for estimating the effectiveness of treatments in real-world populations. It explains how real-world data can directly be used or combined with other data sources to derive overall and individualized estimates of treatment effect. The book explains statistical methods for implementing bias adjustments, conducting evidence synthesis and individualizing treatment effect, whilst also providing illustrative examples and supporting software. The chapters and contents of the book are written by leading experts, with a track record in the generation and/or evaluation of real-world evidence.

This book is intended as a pivotal textbook for statisticians, epidemiologists, methodologists, regulators and/or regulatory scientists considering, undertaking or appraising the real-world evidence of treatment effectiveness. It covers key concepts and stages to derive and evaluate treatment effect estimates for entire populations and specific individuals. The book offers a conceptual framework towards estimating treatment effects at both the population and individualized level, where modelling methods may include traditional regression-based and machine learning methods.

## Motivation

Although randomized clinical trials traditionally form the cornerstone of comparative effectiveness research, there is a growing demand to consider evidence from “real-world data” (RWD) in clinical decision-making. These data are often available from observational cohort studies, administrative databases, and patient registries, and may offer additional insights into the comparative effectiveness and safety of treatments. Yet, the analysis of RWD and the evaluation of real-world evidence face many operational and methodological challenges.

In this book, we aim to address three current needs. First, this book will offer the guidance that is currently lacking on assessing the quality of RWD and on implementing appropriate statistical methods to reduce bias of single study estimates of treatment effects. Second, this book will provide researchers with advanced approaches to pooling estimates from multiple non-randomized studies for which traditional evidence synthesis methods are not suitable.

Finally, to answer the growing need to translate average estimates of treatment effects to individualized clinical decision-making, this book will present recent methods for more tailored approaches where patient characteristics are used to derive their individualized prognosis and treatment benefit.

This book aims to explain key principles and state-of-the-art methods for deriving treatment effects in entire populations and specific individuals using RWD. It will not only discuss statistical theory by key experts in the field; it will also provide illustrative examples and practical guidance for implementation in R. In short, the book aims to prepare a new generation of researchers who wish to generate and integrate evidence from both randomized and non-randomized data sources to investigate the real-world effectiveness of treatments in populations and individual patients.

## Contents

The book is divided into six sections:

1. **Introduction.** This section introduces the relevance of real-world data for conducting comparative effectiveness research, and discusses various concerns regarding their use.
2. **Principles of treatment effect estimation using real-world data.** In this section, we discuss key principles of treatment effect estimation in non-randomized data sources. We explain methods to adjust for confounding (including propensity score analysis and disease risk score analysis) and missing data when estimating the treatment effect for a specific (sub)population.
3. **Principles of evidence synthesis.** In this section, we discuss statistical methods for estimating the treatment effect using (individual participant and/or aggregate) data from multiple studies. To this purpose, key principles of meta-analysis are introduced and explained, including the standard fixed effect and random effects meta-analysis models, methods for individual patient data (IPD) meta-analysis, methods for network meta-analysis, and methods for data-driven and tailored bias adjustment.
4. **Advanced modelling issues for dealing with additional bias in both randomized and non-randomized data sources.** In this section, we discuss advanced statistical and machine learning methods for dealing with time-varying confounding, informative visit schedules, and measurement error.
5. **Individualizing treatment effects for personalized medicine.** In this section, we discuss statistical methods to estimate and evaluate individualized treatment effects.
6. Closing

## 2 Validity control and quality assessment of real-world data and real-world evidence

Christina ReadThomas Debray (Smart Data Analysis and Statistics B.V.)

```
library(readxl)
library(robvis)
```

The quality of real-world data is often suboptimal and can therefore lead to bias when generating real-world evidence (RWE). In this chapter, we will introduce key quality concerns of RWD, including their accuracy, completeness, and timeliness. Subsequently, we will discuss which steps can be taken to assess the quality of RWD, and determine their fitness for use. The chapter will also introduce directed acyclic graphs to explain how the analysis of RWD may be affected by different types of bias. We will put particular focus on confounding bias, selection bias, and information bias, and explain how these biases can be addressed by referring to specific chapters from the book. Finally, the chapter presents common quality appraisal tools that can be used to assess the quality of real-world evidence (for instance when conducting a systematic review).

A risk of bias assessment was conducted in the COVID-NMA review. We can create a summary table of risk of bias assessment and produce a traffic light plot as follows:

```
Risk_of_Bias <- read_excel("resources/RoB-covid.xlsx")

#creation of traffic light plot
trafficlight_rob <- rob_traffic_light(data = Risk_of_Bias, tool = "ROB2")
trafficlight_rob
```

|                            | Risk of bias domains |    |    |    |    |         |
|----------------------------|----------------------|----|----|----|----|---------|
|                            | D1                   | D2 | D3 | D4 | D5 | Overall |
| Abd-Elsalam et al          |                      |    |    |    |    |         |
| Ader                       |                      |    |    |    |    |         |
| Beigel (ACTT-1)            |                      |    |    |    |    |         |
| Cao et al                  |                      |    |    |    |    |         |
| Cavalcanti et al           |                      |    |    |    |    |         |
| Criner*                    |                      |    |    |    |    |         |
| Davoudi-Monfared           |                      |    |    |    |    |         |
| Horby (RECOVERY; DEXA)     |                      |    |    |    |    |         |
| Horby (RECOVERY; LOPI)     |                      |    |    |    |    |         |
| Horby (RECOVERY; TOCI)     |                      |    |    |    |    |         |
| Islam^                     |                      |    |    |    |    |         |
| Lyngbakken et al           |                      |    |    |    |    |         |
| Mahajan                    |                      |    |    |    |    |         |
| Pan (WHO Solidarity; HCQ)  |                      |    |    |    |    |         |
| Pan (WHO Solidarity; INTB) |                      |    |    |    |    |         |
| Pan (WHO Solidarity; LOPI) |                      |    |    |    |    |         |
| Pan (WHO Solidarity; REM)  |                      |    |    |    |    |         |
| Spinner                    |                      |    |    |    |    |         |
| Wang                       |                      |    |    |    |    |         |
| Broman                     |                      |    |    |    |    |         |
| Declerq                    |                      |    |    |    |    |         |
| Gordon (REMAP-CAP)         |                      |    |    |    |    |         |
| Hermine                    |                      |    |    |    |    |         |
| Rohmani                    |                      |    |    |    |    |         |
| Rosas (COVACTA)            |                      |    |    |    |    |         |
| Rutgers                    |                      |    |    |    |    |         |
| Salama(EMPACTA)            |                      |    |    |    |    |         |
| Salvarani*                 |                      |    |    |    |    |         |
| Soin (COVINTOC)            |                      |    |    |    |    |         |
| Stone*                     |                      |    |    |    |    |         |
| Tomazini                   |                      |    |    |    |    |         |
| Talaschian                 |                      |    |    |    |    |         |
| Ulrich et al               |                      |    |    |    |    |         |
| Veiga                      |                      |    |    |    |    |         |

Study

Domains:  
D1: Bias arising from the randomization process.  
D2: Bias due to deviations from intended intervention.  
D3: Bias due to missing outcome data.  
D4: Bias in measurement of the outcome.  
D5: Bias in selection of the reported result.

Judgement  
 High  
 Some concerns  
 Low



## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19045)
```

```
Matrix products: default
```

```
locale:
```

```
[1] LC_COLLATE=Dutch_Netherlands.utf8 LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

```
attached base packages:
```

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

```
other attached packages:
```

```
[1] robvis_0.3.0.900 readxl_1.4.2
```

```
loaded via a namespace (and not attached):
```

```
[1] digest_0.6.31    cellranger_1.1.0 jsonlite_1.8.4    magrittr_2.0.3
[5] evaluate_0.21    rlang_1.1.0      cli_3.6.1         rstudioapi_0.14
[9] rmarkdown_2.21   tools_4.2.3      xfun_0.39         yaml_2.3.7
[13] fastmap_1.1.1    compiler_4.2.3   htmltools_0.5.5   knitr_1.42
```

### 3 Confounding adjustment using propensity score methods

Tammy Jiang (Biogen)

Thomas Debray (Smart Data Analysis and Statistics B.V.)

The purpose of this document is to provide example R code that demonstrates how to estimate the propensity score and implement matching, stratification, weighting, and regression adjustment for the continuous propensity score. In this example using simulated data, we have two disease modifying therapies (DMT1 and DMT0) and the outcome is the number of post-treatment multiple sclerosis relapses during follow-up. We will estimate the average treatment effect in the treated (ATT) using propensity score matching, stratification, and weighting. We will estimate the average treatment effect in the population (ATE) using regression adjustment for the continuous propensity score. The treatment effects can be interpreted as annualized relapse rate ratios (ARR).

We consider an example dataset with the following characteristics:

```
head(dat)
```

|    | age | female | prevDMT | efficacy | premedicalcost | numSymptoms | prerelapse_num |
|----|-----|--------|---------|----------|----------------|-------------|----------------|
| 1: | 50  | 1      |         | None     | 3899.61        | 1           | 1              |
| 2: | 51  | 0      |         | None     | 9580.51        | 1           | 0              |
| 3: | 56  | 0      |         | None     | 4785.89        | 1           | 0              |
| 4: | 44  | 1      |         | None     | 8696.80        | 1           | 1              |
| 5: | 63  | 0      |         | None     | 2588.03        | 1           | 0              |
| 6: | 28  | 1      |         | None     | 5435.57        | 1           | 0              |

|    | treatment | y | years      | Iscore      |
|----|-----------|---|------------|-------------|
| 1: | DMT1      | 0 | 1.78507871 | Moderate A1 |
| 2: | DMT1      | 0 | 0.01368925 | High A1     |
| 3: | DMT1      | 2 | 3.25530459 | High A1     |
| 4: | DMT1      | 2 | 5.73853525 | Neutral     |
| 5: | DMT1      | 0 | 1.31143053 | High A1     |
| 6: | DMT1      | 0 | 0.59137577 | Moderate A0 |

## 3.1 Comparing baseline characteristics

- DMT1 is the treatment group and DMT0 is the control group
- prevDMTefficacy is previous DMT efficacy (none, low efficacy, and medium/high efficacy)
- prerelapse\_num is the number of previous MS relapses

|                            | DMT0         | DMT1         |
|----------------------------|--------------|--------------|
| n                          | 2300         | 7700         |
| age (mean (SD))            | 51.39 (8.32) | 44.25 (9.79) |
| female = 1 (%)             | 1671 (72.65) | 5915 (76.82) |
| prevDMTefficacy (%)        |              |              |
| None                       | 1247 (54.22) | 3171 (41.18) |
| Low_efficacy               | 261 (11.35)  | 858 (11.14)  |
| Medium_high_efficacy       | 792 (34.43)  | 3671 (47.68) |
| prerelapse_num (mean (SD)) | 0.39 (0.62)  | 0.46 (0.68)  |

## 3.2 Estimating the propensity score

### 3.2.1 Logistic regression

We sought to restore balance in the distribution of baseline covariates in patients treated with DMT1 (index treatment) and DMT0 (control treatment). We fit a multivariable logistic regression model in which treatment was regressed on baseline characteristics including age, sex, previous DMT efficacy, and previous number of relapses.

```
# Fit logistic regression model
ps.model <- glm(treatment ~ age + female + prevDMTefficacy + prerelapse_num,
               data = dat, family = binomial())

# Summary of logistic regression model
summary(ps.model)
```

Call:

```
glm(formula = treatment ~ age + female + prevDMTefficacy + prerelapse_num,
     family = binomial(), data = dat)
```

Deviance Residuals:

| Min     | 1Q     | Median | 3Q     | Max    |
|---------|--------|--------|--------|--------|
| -2.7949 | 0.2585 | 0.5220 | 0.7478 | 1.5033 |

Coefficients:

|                                     | Estimate  | Std. Error | z value | Pr(> z )     |
|-------------------------------------|-----------|------------|---------|--------------|
| (Intercept)                         | 4.809473  | 0.157127   | 30.609  | < 2e-16 ***  |
| age                                 | -0.086708 | 0.002996   | -28.939 | < 2e-16 ***  |
| female1                             | 0.253611  | 0.057664   | 4.398   | 1.09e-05 *** |
| prevDMTefficacyLow_efficacy         | 0.310394  | 0.083022   | 3.739   | 0.000185 *** |
| prevDMTefficacyMedium_high_efficacy | 0.660266  | 0.054393   | 12.139  | < 2e-16 ***  |
| prerelapse_num                      | 0.156318  | 0.039288   | 3.979   | 6.93e-05 *** |

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 10786 on 9999 degrees of freedom  
 Residual deviance: 9597 on 9994 degrees of freedom  
 AIC: 9609

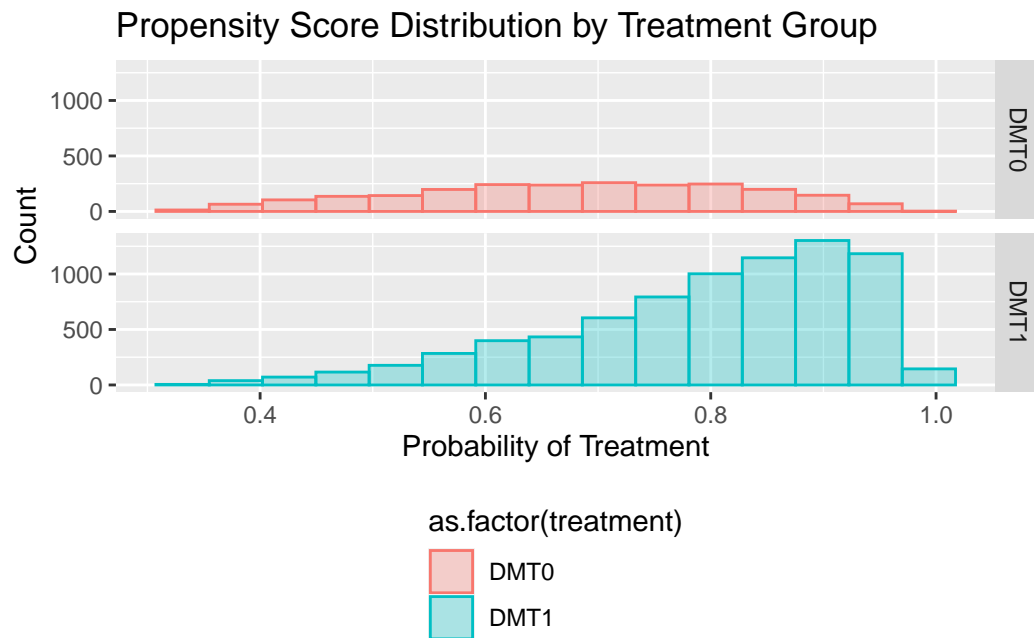
Number of Fisher Scoring iterations: 5

```
# Extract propensity scores
dat$ps <- predict(ps.model, data = dat, type = "response")
```

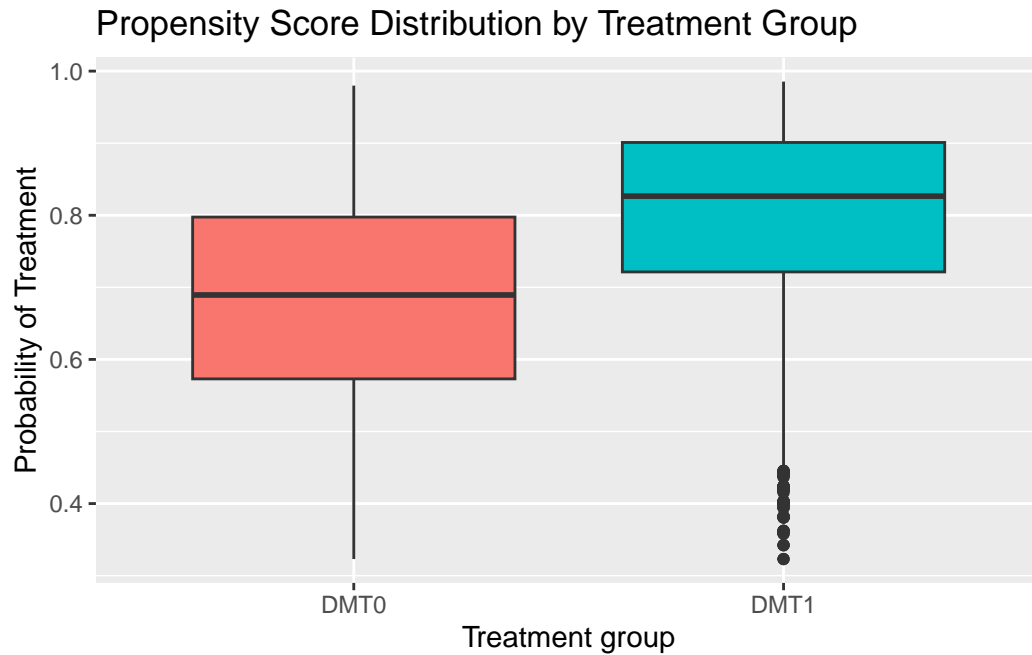
### 3.2.2 Assessing overlap

We examined the degree of overlap in the distribution of propensity scores across treatment groups using histograms and side-by-side box plots.

```
# Histogram
ggplot(dat, aes(x = ps, fill = as.factor(treatment), color = as.factor(treatment))) +
  geom_histogram(alpha = 0.3, position='identity', bins = 15) +
  facet_grid(as.factor(treatment) ~ .) +
  xlab("Probability of Treatment") +
  ylab("Count") +
  ggtitle("Propensity Score Distribution by Treatment Group") +
  theme(legend.position = "bottom", legend.direction = "vertical")
```



```
# Side-by-side box plots
ggplot(dat, aes(x=as.factor(treatment), y=ps, fill=as.factor(treatment))) +
  geom_boxplot() +
  ggtitle("Propensity Score Distribution by Treatment Group") +
  ylab("Probability of Treatment") +
  xlab("Treatment group") +
  theme(legend.position = "none")
```



```
# Distribution of propensity scores by treatment groups
summary(dat$ps[dat$treatment == "DMT1"])
```

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.3230  0.7214  0.8265  0.7970  0.9010  0.9854
```

```
summary(dat$ps[dat$treatment == "DMT0"])
```

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.3230  0.5730  0.6894  0.6795  0.7975  0.9799
```

## 3.3 Propensity score matching

### 3.3.1 1:1 Optimal full matching without replacement

```
library(MatchIt)

# Use MatchIt package for PS matching
opt <- matchit(treatment ~ age + female + prevDMTefficacy + prerelapse_num,
              data = dat,
              method = "full",
              estimand = "ATT")

opt
```

A matchit object

- method: Optimal full matching
- distance: Propensity score
  - estimated with logistic regression
- number of obs.: 10000 (original), 10000 (matched)
- target estimand: ATT
- covariates: age, female, prevDMTefficacy, prerelapse\_num

### 3.3.2 Assess balance after matching

```
summary(opt)
```

Call:

```
matchit(formula = treatment ~ age + female + prevDMTefficacy +
        prerelapse_num, data = dat, method = "full", estimand = "ATT")
```

Summary of Balance for All Data:

|                             | Means Treated | Means Control | Std. Mean Diff. |
|-----------------------------|---------------|---------------|-----------------|
| distance                    | 0.7970        | 0.6795        | 0.8943          |
| age                         | 44.2496       | 51.3883       | -0.7289         |
| female0                     | 0.2318        | 0.2735        | -0.0987         |
| female1                     | 0.7682        | 0.7265        | 0.0987          |
| prevDMTefficacyNone         | 0.4118        | 0.5422        | -0.2649         |
| prevDMTefficacyLow_efficacy | 0.1114        | 0.1135        | -0.0065         |

|                                     |            |           |          |
|-------------------------------------|------------|-----------|----------|
| prevDMTefficacyMedium_high_efficacy | 0.4768     | 0.3443    | 0.2651   |
| prerelapse_num                      | 0.4595     | 0.3930    | 0.0976   |
|                                     | Var. Ratio | eCDF Mean | eCDF Max |
| distance                            | 0.7873     | 0.1917    | 0.3379   |
| age                                 | 1.3868     | 0.1519    | 0.3085   |
| female0                             | .          | 0.0417    | 0.0417   |
| female1                             | .          | 0.0417    | 0.0417   |
| prevDMTefficacyNone                 | .          | 0.1304    | 0.1304   |
| prevDMTefficacyLow_efficacy         | .          | 0.0020    | 0.0020   |
| prevDMTefficacyMedium_high_efficacy | .          | 0.1324    | 0.1324   |
| prerelapse_num                      | 1.1990     | 0.0133    | 0.0383   |

Summary of Balance for Matched Data:

|                                     |                 |               |                 |
|-------------------------------------|-----------------|---------------|-----------------|
|                                     | Means Treated   | Means Control | Std. Mean Diff. |
| distance                            | 0.7970          | 0.7970        | 0.0003          |
| age                                 | 44.2496         | 44.3185       | -0.0070         |
| female0                             | 0.2318          | 0.2275        | 0.0101          |
| female1                             | 0.7682          | 0.7725        | -0.0101         |
| prevDMTefficacyNone                 | 0.4118          | 0.4130        | -0.0024         |
| prevDMTefficacyLow_efficacy         | 0.1114          | 0.0893        | 0.0703          |
| prevDMTefficacyMedium_high_efficacy | 0.4768          | 0.4977        | -0.0419         |
| prerelapse_num                      | 0.4595          | 0.4399        | 0.0288          |
|                                     | Var. Ratio      | eCDF Mean     | eCDF Max        |
| distance                            | 0.9976          | 0.0005        | 0.0075          |
| age                                 | 1.0392          | 0.0038        | 0.0153          |
| female0                             | .               | 0.0043        | 0.0043          |
| female1                             | .               | 0.0043        | 0.0043          |
| prevDMTefficacyNone                 | .               | 0.0012        | 0.0012          |
| prevDMTefficacyLow_efficacy         | .               | 0.0221        | 0.0221          |
| prevDMTefficacyMedium_high_efficacy | .               | 0.0209        | 0.0209          |
| prerelapse_num                      | 1.1319          | 0.0060        | 0.0229          |
|                                     | Std. Pair Dist. |               |                 |
| distance                            | 0.0008          |               |                 |
| age                                 | 0.0667          |               |                 |
| female0                             | 0.1775          |               |                 |
| female1                             | 0.1775          |               |                 |
| prevDMTefficacyNone                 | 0.1100          |               |                 |
| prevDMTefficacyLow_efficacy         | 0.1846          |               |                 |
| prevDMTefficacyMedium_high_efficacy | 0.1614          |               |                 |
| prerelapse_num                      | 0.2170          |               |                 |

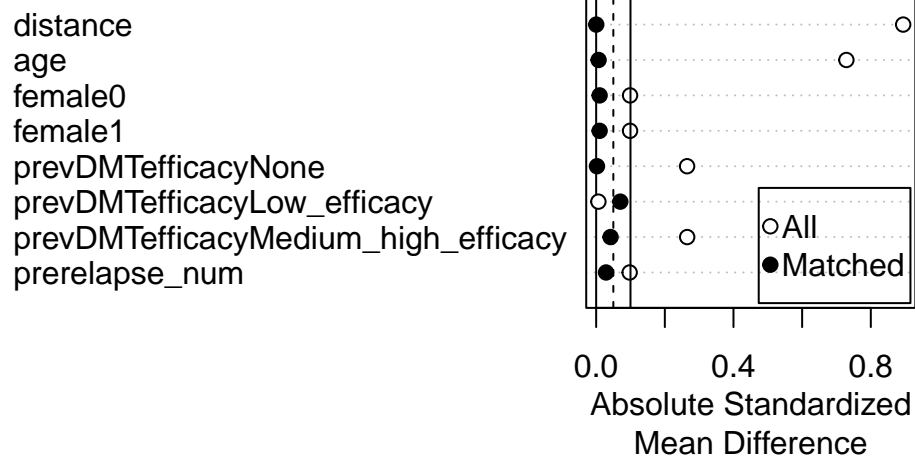
Sample Sizes:

|         |         |
|---------|---------|
| Control | Treated |
|---------|---------|

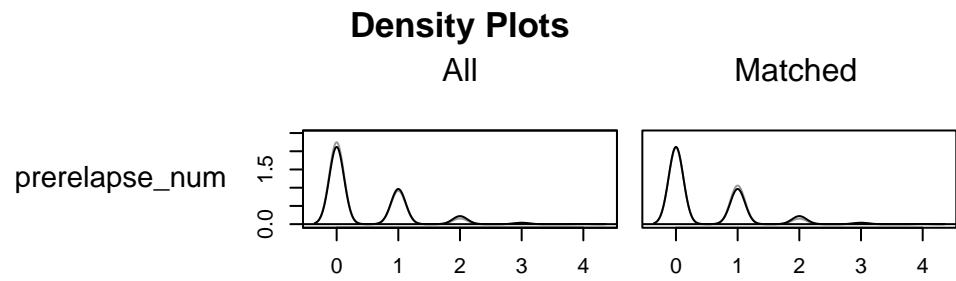
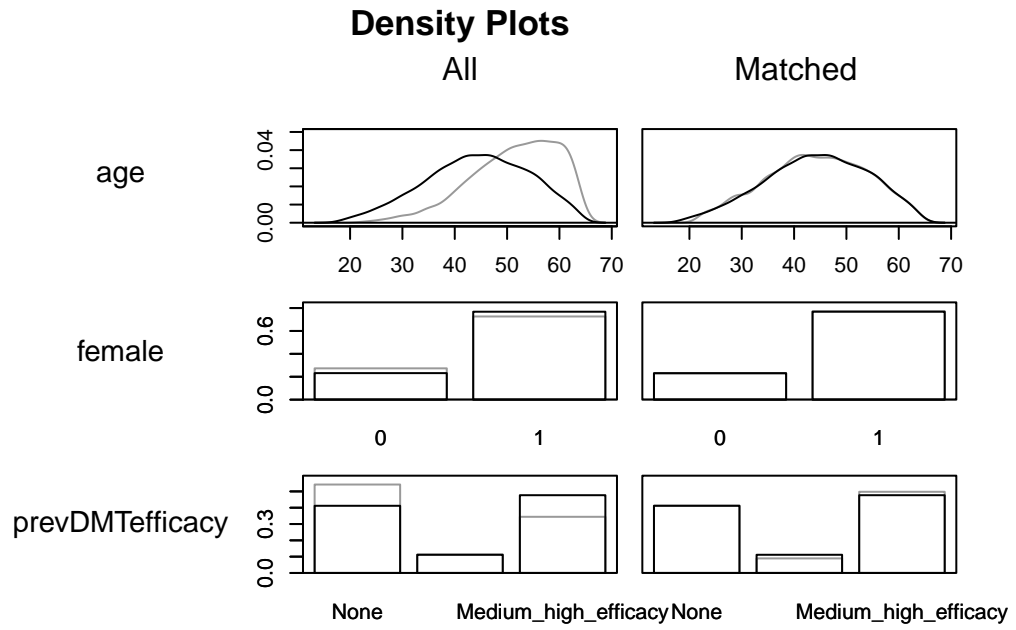


|               |        |      |
|---------------|--------|------|
| All           | 2300.  | 7700 |
| Matched (ESS) | 307.06 | 7700 |
| Matched       | 2300.  | 7700 |
| Unmatched     | 0.     | 0    |
| Discarded     | 0.     | 0    |

```
plot(summary(opt))
```



```
# black line is treated group, grey line is control group
plot(opt, type = "density", which.xs = vars)
```



### 3.3.3 Estimating the ATT

We can estimate the ATT in the matched sample using Poisson regression in which the number of post-treatment relapses is regressed on treatment status and follow-up time for each patient (captured by the variable `years`). More details are provided at <https://cran.r-project.org/web/packages/MatchIt/vignettes/estimating-effects.html>.

```
# Matched data
matched.data <- match.data(opt)

# Poisson regression model
opt.fit <- glm(y ~ treatment + offset(log(years)),
              family = poisson(link = "log"),
              data = matched.data,
              weights = weights)

# Treatment effect estimation
opt.comp <- comparisons(opt.fit,
                        variables = "treatment",
                        vcov = ~subclass,
                        newdata = subset(matched.data, treatment == "DMT1"),
                        wts = "weights",
                        transform_pre = "ratio")

opt.comp |> tidy()
```

# A tibble: 1 x 8

|   | term      | contrast    | estimate | std.error | statistic | p.value  | conf.low | conf.high |
|---|-----------|-------------|----------|-----------|-----------|----------|----------|-----------|
|   | <chr>     | <chr>       | <dbl>    | <dbl>     | <dbl>     | <dbl>    | <dbl>    | <dbl>     |
| 1 | treatment | mean(DMT1)~ | 0.804    | 0.102     | 7.88      | 3.25e-15 | 0.604    | 1.00      |

As indicated in the summary output above, the annualized relapse rate ratio for DMT1 vs DMT0 among patients treated with DMT0 (ATT) is given as 0.8 with a 95% confidence interval ranging from 0.6 to 1.

## 3.4 Propensity score stratification

### 3.4.1 Divide sample into quintiles of propensity scores

We will form five mutually exclusive groups of the estimated propensity score.

```
# Create five strata
dat <- dat %>% mutate(ps.strata = cut(ps,
                                     breaks = c(quantile(ps, probs=seq(0,1,0.2))),
                                     labels = seq(1:5),
                                     include.lowest = TRUE))

# Number of patients in each stratum
table(dat$ps.strata)
```

```
1      2      3      4      5
2002 2015 1991 1997 1995
```

### 3.4.2 Assess balance within each propensity score stratum

Within each propensity score stratum, treated and control patients should have similar values of the propensity score and the distribution of baseline covariates should be approximately balanced between treatment groups.

#### 3.4.2.1 Propensity Score Stratum #1

```
tab1.strata1 <- CreateTableOne(vars, data = dat %>% filter(ps.strata == 1),
                              factorVars = c("female", "prevDMTefficacy"),
                              strata = "treatment", test = FALSE)

tab1.strata1.print <- print(tab1.strata1, catDigits = 2, contDigits = 2,
                             smd = TRUE)
```

|                            | DMT0         | DMT1         | SMD   |
|----------------------------|--------------|--------------|-------|
| n                          | 901          | 1101         |       |
| age (mean (SD))            | 58.38 (3.67) | 57.45 (3.73) | 0.251 |
| female = 1 (%)             | 605 (67.15)  | 775 (70.39)  | 0.070 |
| prevDMTefficacy (%)        |              |              | 0.056 |
| None                       | 650 (72.14)  | 771 (70.03)  |       |
| Low_efficacy               | 106 (11.76)  | 130 (11.81)  |       |
| Medium_high_efficacy       | 145 (16.09)  | 200 (18.17)  |       |
| prerelapse_num (mean (SD)) | 0.29 (0.53)  | 0.33 (0.56)  | 0.074 |

### 3.4.2.2 Propensity Score Stratum #2

```
tab1.strata2 <- CreateTableOne(vars, data = dat %>% filter(ps.strata == 2),  
                               factorVars = c("female", "prevDMTefficacy"),  
                               strata = "treatment", test = FALSE)  
  
tab1.strata2.print <- print(tab1.strata2, catDigits = 2, contDigits = 2,  
                             smd = TRUE)
```

|                            | DMT0         | DMT1         | SMD   |
|----------------------------|--------------|--------------|-------|
| n                          | 617          | 1398         |       |
| age (mean (SD))            | 52.18 (4.35) | 51.97 (4.22) | 0.049 |
| female = 1 (%)             | 458 (74.23)  | 1048 (74.96) | 0.017 |
| prevDMTefficacy (%)        |              |              | 0.054 |
| None                       | 292 (47.33)  | 624 (44.64)  |       |
| Low_efficacy               | 69 (11.18)   | 162 (11.59)  |       |
| Medium_high_efficacy       | 256 (41.49)  | 612 (43.78)  |       |
| prerelapse_num (mean (SD)) | 0.40 (0.64)  | 0.41 (0.66)  | 0.004 |

### 3.4.2.3 Propensity Score Stratum #3

```
tab1.strata3 <- CreateTableOne(vars, data = dat %>% filter(ps.strata == 3),  
                               factorVars = c("female", "prevDMTefficacy"),  
                               strata = "treatment", test = FALSE)  
  
tab1.strata3.print <- print(tab1.strata3, catDigits = 2, contDigits = 2,  
                             smd = TRUE)
```

|                            | DMT0         | DMT1         | SMD   |
|----------------------------|--------------|--------------|-------|
| n                          | 392          | 1599         |       |
| age (mean (SD))            | 46.73 (4.06) | 46.36 (4.08) | 0.092 |
| female = 1 (%)             | 305 (77.81)  | 1193 (74.61) | 0.075 |
| prevDMTefficacy (%)        |              |              | 0.041 |
| None                       | 168 (42.86)  | 687 (42.96)  |       |
| Low_efficacy               | 52 (13.27)   | 191 (11.94)  |       |
| Medium_high_efficacy       | 172 (43.88)  | 721 (45.09)  |       |
| prerelapse_num (mean (SD)) | 0.49 (0.68)  | 0.47 (0.66)  | 0.031 |

#### 3.4.2.4 Propensity Score Stratum #4

```
tab1.strata4 <- CreateTableOne(vars, data = dat %>% filter(ps.strata == 4),  
                               factorVars = c("female", "prevDMTefficacy"),  
                               strata = "treatment", test = FALSE)  
  
tab1.strata4.print <- print(tab1.strata4, catDigits = 2, contDigits = 2,  
                             smd = TRUE)
```

|                            | DMT0         | DMT1         | SMD   |
|----------------------------|--------------|--------------|-------|
| n                          | 269          | 1728         |       |
| age (mean (SD))            | 41.07 (4.11) | 40.88 (4.29) | 0.046 |
| female = 1 (%)             | 203 (75.46)  | 1356 (78.47) | 0.071 |
| prevDMTefficacy (%)        |              |              | 0.084 |
| None                       | 105 (39.03)  | 634 (36.69)  |       |
| Low_efficacy               | 22 ( 8.18)   | 181 (10.47)  |       |
| Medium_high_efficacy       | 142 (52.79)  | 913 (52.84)  |       |
| prerelapse_num (mean (SD)) | 0.50 (0.69)  | 0.51 (0.71)  | 0.012 |

#### 3.4.2.5 Propensity Score Stratum #5

```
tab1.strata5 <- CreateTableOne(vars, data = dat %>% filter(ps.strata == 5),  
                               factorVars = c("female", "prevDMTefficacy"),  
                               strata = "treatment", test = FALSE)  
  
tab1.strata5.print <- print(tab1.strata5, catDigits = 2, contDigits = 2,  
                             smd = TRUE)
```

|                            | DMT0         | DMT1         | SMD   |
|----------------------------|--------------|--------------|-------|
| n                          | 121          | 1874         |       |
| age (mean (SD))            | 33.26 (4.95) | 32.04 (5.58) | 0.233 |
| female = 1 (%)             | 100 (82.64)  | 1543 (82.34) | 0.008 |
| prevDMTefficacy (%)        |              |              | 0.050 |
| None                       | 32 (26.45)   | 455 (24.28)  |       |
| Low_efficacy               | 12 ( 9.92)   | 194 (10.35)  |       |
| Medium_high_efficacy       | 77 (63.64)   | 1225 (65.37) |       |
| prerelapse_num (mean (SD)) | 0.52 (0.66)  | 0.52 (0.73)  | 0.004 |

### 3.4.3 Estimating and pooling of stratum-specific treatment effects

The overall ATT across strata can be estimated by weighting stratum-specific estimates by the proportion of treated patients in each stratum over all treated patients in the sample.

We first define a function `att.strata.function()` to calculate stratum-specific estimates of the treatment effect:

```
att.strata.function <- function(data, stratum, confint = TRUE) {  
  
  fit <- glm("y ~ treatment + offset(log(years))",  
            family = poisson(link = "log"),  
            data = data %>% filter(ps.strata == stratum))  
  
  arr <- round(as.numeric(exp(coef(fit)["treatmentDMT1"])), digits = 3)  
  ll <- ul <- NA  
  
  if (confint) {  
    ll <- round(exp(confint(fit))["treatmentDMT1",1], digits = 3)  
    ul <- round(exp(confint(fit))["treatmentDMT1",2], digits = 3)  
  }  
  
  return(c("stratum" = stratum,  
          "arr" = arr,  
          "ci_lower" = ll,  
          "ci_upper" = ul))  
}  
  
arr.strata <- as.data.frame(t(apply(1:5, att.strata.function, data = dat)))  
arr.strata
```

|   | stratum | arr   | ci_lower | ci_upper |
|---|---------|-------|----------|----------|
| 1 | 1       | 0.904 | 0.760    | 1.076    |
| 2 | 2       | 0.822 | 0.696    | 0.975    |
| 3 | 3       | 0.798 | 0.666    | 0.961    |
| 4 | 4       | 0.716 | 0.587    | 0.881    |
| 5 | 5       | 0.589 | 0.463    | 0.761    |

Subsequently, we define a function `weights.strata.function()` to calculate the weights for each stratum. The weight is the proportion of treated patients in each stratum over all treated patients in the sample:

```

weights.strata.function <- function(data, stratum) {
  n_DMT1_stratum <- nrow(data %>% filter(ps.strata == stratum & treatment == "DMT1"))
  n_DMT1_all <- nrow(data %>% filter(treatment == "DMT1"))
  weight <- n_DMT1_stratum/n_DMT1_all
  return(c("stratum" = stratum, "weight" = weight))
}

weights.strata <- as.data.frame(t(apply(1:5, weights.strata.function, data = dat)))
weights.strata

```

```

stratum    weight
1          1 0.1429870
2          2 0.1815584
3          3 0.2076623
4          4 0.2244156
5          5 0.2433766

```

```

# Create table with ARRs and weights for each PS stratum
arr.weights.merged <- merge(arr.strata, weights.strata, by = "stratum")

# Calculate the weighted ARR for each stratum
arr.weights.merged <- arr.weights.merged %>%
  mutate(weighted.arr = as.numeric(arr) * weight)

# Sum the weighted ARRs across strata to get the overall ATT
sum(arr.weights.merged$weighted.arr)

```

```
[1] 0.7482462
```

We now define a new function `ps.stratification.bootstrap()` that integrates estimation of the ATT and the PS weights for bootstrapping purposes:

```

ps.stratification.bootstrap <- function(data, inds) {
  d <- data[inds,]

  d$ps.strata <- cut(d$ps,
    breaks = c(quantile(dat$ps, probs = seq(0, 1, by = 0.2))),
    labels = seq(5),
    include.lowest = TRUE)

```



```

arr.strata <- as.data.frame(t(sapply(1:5, att.strata.function,
                                   data = d, confint = FALSE)))

weights.strata <- as.data.frame(t(sapply(1:5, weights.strata.function, data = d)))

return(arr.strata$arr[1] * weights.strata$weight[1] +
       arr.strata$arr[2] * weights.strata$weight[2] +
       arr.strata$arr[3] * weights.strata$weight[3] +
       arr.strata$arr[4] * weights.strata$weight[4] +
       arr.strata$arr[5] * weights.strata$weight[5])
}

```

We can now estimate the treatment effect and its confidence interval using the bootstrap procedure:

```
library(boot)
```

Attaching package: 'boot'

The following object is masked from 'package:survival':

```
aml
```

```

set.seed(1854)
arr.stratification.boot <- boot(data = dat,
                               statistic = ps.stratification.bootstrap,
                               R = 1000)

# Bootstrapped ARR
median(arr.stratification.boot$t)

```

```
[1] 0.7558609
```

```

# Bootstrapped ARR 95% CI
quantile(arr.stratification.boot$t[,1], c(0.025, 0.975))

```

```

      2.5%      97.5%
0.6835885 0.8362947

```

## 3.5 Propensity score weighting

### 3.5.1 Calculate propensity score weights for ATT

Propensity score weighting reweights the study sample to generate an artificial population (i.e., pseudo-population) in which the covariates are no longer associated with treatment, thereby removing confounding by measured covariates. For the ATT, the weight for all treated patients is set to one. Conversely, the weight for patients in the control group is set to the propensity score divided by one minus the propensity score, that is,  $(PS/(1 - PS))$ . We estimated stabilized weights to address extreme weights.

```
library(WeightIt)

w.out <- weightit(treatment ~ age + female + prevDMTefficacy + prerelapse_num,
                  data = dat,
                  method = "ps",
                  estimand = "ATT")
                  #stabilize = TRUE)

w.out
```

A weightit object

- method: "glm" (propensity score weighting with GLM)
- number of obs.: 10000
- sampling weights: none
- treatment: 2-category
- estimand: ATT (focal: DMT1)
- covariates: age, female, prevDMTefficacy, prerelapse\_num

```
summary(w.out)
```

#### Summary of weights

- Weight ranges:

|      | Min    | Max     |
|------|--------|---------|
| DMT0 | 0.4772 | 48.6856 |
| DMT1 | 1.0000 | 1.0000  |

- Units with the 5 most extreme weights by group:

|      |         |         |         |         |         |
|------|---------|---------|---------|---------|---------|
|      | 9492    | 8836    | 6544    | 9610    | 4729    |
| DMT0 | 32.1027 | 32.1027 | 34.3126 | 38.1817 | 48.6856 |
|      | 8       | 7       | 4       | 2       | 1       |
| DMT1 | 1       | 1       | 1       | 1       | 1       |

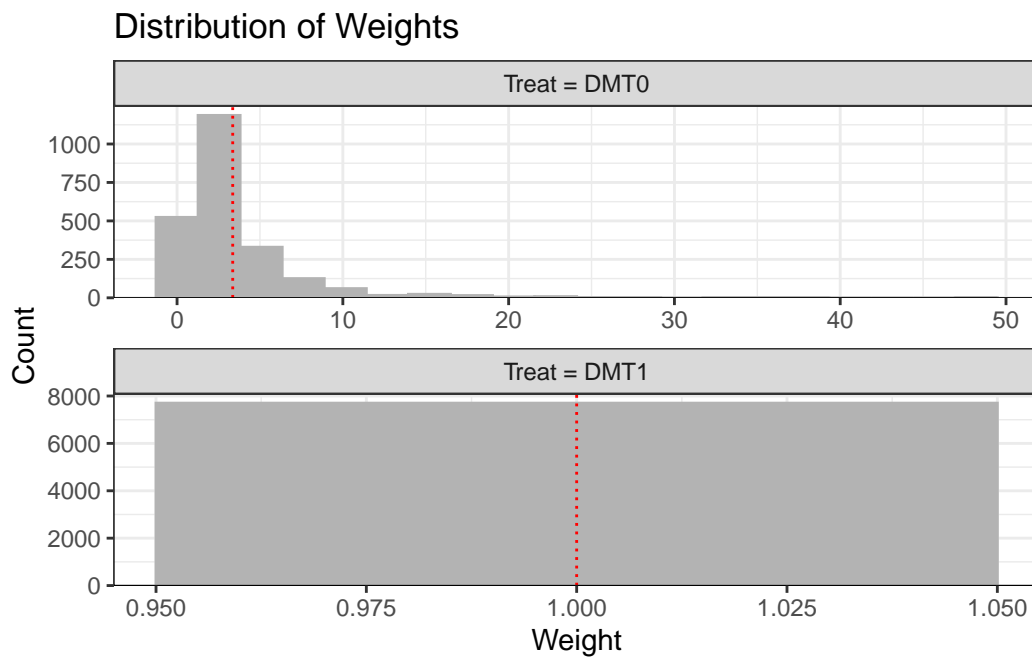
- Weight statistics:

|      |             |       |         |         |
|------|-------------|-------|---------|---------|
|      | Coef of Var | MAD   | Entropy | # Zeros |
| DMT0 | 1.098       | 0.673 | 0.383   | 0       |
| DMT1 | 0.000       | 0.000 | -0.000  | 0       |

- Effective Sample Sizes:

|            |         |      |
|------------|---------|------|
|            | DMT0    | DMT1 |
| Unweighted | 2300.   | 7700 |
| Weighted   | 1043.16 | 7700 |

```
plot(summary(w.out))
```



### 3.5.2 Assess balance in the weighted sample

```
bal.tab(w.out, stats = c("m", "v"), thresholds = c(m = .05))
```

#### Balance Measures

|                                      | Type        | Diff.Adj | M.Threshold     |
|--------------------------------------|-------------|----------|-----------------|
| prop.score                           | Distance    | -0.0045  | Balanced, <0.05 |
| age                                  | Contin.     | 0.0054   | Balanced, <0.05 |
| female                               | Binary      | 0.0005   | Balanced, <0.05 |
| prevDMTefficacy_None                 | Binary      | -0.0003  | Balanced, <0.05 |
| prevDMTefficacy_Low_efficacy         | Binary      | 0.0023   | Balanced, <0.05 |
| prevDMTefficacy_Medium_high_efficacy | Binary      | -0.0020  | Balanced, <0.05 |
| prerelapse_num                       | Contin.     | -0.0034  | Balanced, <0.05 |
|                                      | V.Ratio.Adj |          |                 |
| prop.score                           |             | 0.9926   |                 |
| age                                  |             | 1.0102   |                 |
| female                               |             | .        |                 |
| prevDMTefficacy_None                 |             | .        |                 |
| prevDMTefficacy_Low_efficacy         |             | .        |                 |
| prevDMTefficacy_Medium_high_efficacy |             | .        |                 |
| prerelapse_num                       |             | 1.0941   |                 |

#### Balance tally for mean differences

|                     | count |
|---------------------|-------|
| Balanced, <0.05     | 7     |
| Not Balanced, >0.05 | 0     |

#### Variable with the greatest mean difference

| Variable | Diff.Adj | M.Threshold     |
|----------|----------|-----------------|
| age      | 0.0054   | Balanced, <0.05 |

#### Effective sample sizes

|            | DMT0    | DMT1 |
|------------|---------|------|
| Unadjusted | 2300.   | 7700 |
| Adjusted   | 1043.16 | 7700 |

### 3.5.3 Estimate the ATT

One way to estimate the ATT is to use the survey package. The function `svyglm()` generates model-robust (Horvitz-Thompson-type) standard errors by default, and thus does not require additional adjustments.

```
library(survey)

weighted.data <- svydesign(ids = ~1, data = dat, weights = ~w.out$weights)

weighted.fit <- svyglm(y ~ treatment + offset(log(years)),
                      family = poisson(link = "log"),
                      design = weighted.data)

exp(coef(weighted.fit)["treatmentDMT1"])
```

```
treatmentDMT1
0.7083381
```

```
exp(confint(weighted.fit))["treatmentDMT1",]
```

```
      2.5 %      97.5 %
0.6245507 0.8033662
```

As indicated above, propensity score weighting yielded an ATT estimate of 0.71 (95% CI: 0.66; 0.76).

An alternative approach is to use `glm()` to estimate the treatment effect and calculate robust standard errors.

```
# Alternative way to estimate treatment effect
weighted.fit2 <- glm(y ~ treatment + offset(log(years)),
                    family = poisson(link = "log"),
                    data = dat,
                    weights = w.out$weights)

# Extract the estimated ARR
exp(coef(weighted.fit2))["treatmentDMT1"]
```

```
treatmentDMT1
0.7083381
```

```
# Calculate robust standard error and p-value of the log ARR
coeftest(weighted.fit2, vcov. = vcovHC)["treatmentDMT1",]
```

| Estimate      | Std. Error   | z value       | Pr(> z )     |
|---------------|--------------|---------------|--------------|
| -3.448337e-01 | 6.442745e-02 | -5.352280e+00 | 8.685284e-08 |

```
# Derive 95% confidence interval of the ARR
exp(lmtest::coefci(weighted.fit2,
  level = 0.95, # 95% confidence interval
  vcov. = vcovHC)["treatmentDMT1",])
```

| 2.5 %     | 97.5 %    |
|-----------|-----------|
| 0.6243094 | 0.8036767 |

Using this approach, the ATT estimate was 0.71 (95% CI: 0.62; 0.8).

### 3.6 Regression adjustment for the propensity score for the ATE

In this approach, a regression model is fitted to describe the observed outcome as a function of the received treatment and the estimated propensity score:

```
ps.reg.fit <- glm(y ~ treatment + ps + offset(log(years)),
  family = poisson(link = "log"),
  data = dat)

summary(ps.reg.fit)
```

Call:

```
glm(formula = y ~ treatment + ps + offset(log(years)), family = poisson(link = "log"),
  data = dat)
```

Deviance Residuals:

| Min     | 1Q      | Median  | 3Q      | Max    |
|---------|---------|---------|---------|--------|
| -2.0160 | -0.7336 | -0.4441 | -0.1352 | 4.2634 |

Coefficients:

|               | Estimate | Std. Error | z value | Pr(> z )     |
|---------------|----------|------------|---------|--------------|
| (Intercept)   | -1.99585 | 0.10359    | -19.266 | < 2e-16 ***  |
| treatmentDMT1 | -0.25598 | 0.04431    | -5.777  | 7.60e-09 *** |
| ps            | 1.07521  | 0.13878    | 7.748   | 9.36e-15 *** |

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 7514.7 on 9999 degrees of freedom  
Residual deviance: 7443.0 on 9997 degrees of freedom  
AIC: 12378

Number of Fisher Scoring iterations: 6

```
# ATE
exp(coef(ps.reg.fit))["treatmentDMT1"]
```

```
treatmentDMT1
0.7741606
```

Waiting for profiling to be done...

Waiting for profiling to be done...

Bootstrapped confidence intervals can be obtained as follows:

```
# Function to bootstrap for 95% CIs
ps.reg.bootstrap <- function(data, inds) {
  d <- data[inds,]

  fit <- glm(y ~ treatment + ps + offset(log(years)),
            family = poisson(link = "log"),
            data = d)

  return(exp(coef(fit))["treatmentDMT1"])
}

set.seed(1854)

# Generate 1000 bootstrap replicates
arr.boot <- boot(dat, statistic = ps.reg.bootstrap, R = 1000)

# Extract the median annualized relapse rate across 1000 bootstrap replicates
median(arr.boot$t)
```

```
[1] 0.7750426
```

```
# Take 2.5th and 97.5th percentiles to be 95% CI
quantile(arr.boot$t[,1], c(0.025, 0.975))
```

```
      2.5%      97.5%
0.7010540 0.8545169
```

## 3.7 Overview

| Method   | Estimand | Estimate  | 95% CI<br>(lower) | 95% CI<br>(upper) |
|--|----------|-----------|-------------------|-------------------|
| Optimal full matching                                | ATT      | 0.8039901 | 0.6040414         | 1.0039388         |
| Propensity score stratification                      | ATT      | 0.7482462 | NA                | NA                |
| Propensity score stratification (with bootstrapping) | ATT      | 0.7558609 | 0.6835885         | 0.8362947         |
| Propensity score weighting                           | ATT      | 0.7083381 | 0.6245507         | 0.8033662         |
| Propensity score weighting (robust SE)               | ATT      | 0.7083381 | 0.6243094         | 0.8036767         |
| PS regression adjustment                             | ATE      | 0.7741606 | 0.7101080         | 0.8448218         |
| PS regression adjustment (bootstrapping)             | ATE      | 0.7750426 | 0.7010540         | 0.8545169         |

## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19044)
```

```
Matrix products: default
```

```
locale:
[1] LC_COLLATE=Dutch_Netherlands.utf8 LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

```
attached base packages:
[1] grid      stats      graphics  grDevices  utils      datasets  methods
[8] base
```



other attached packages:

|                        |                        |                 |
|------------------------|------------------------|-----------------|
| [1] WeightIt_0.14.1    | boot_1.3-28.1          | MatchIt_4.5.3   |
| [4] sandwich_3.0-2     | truncnorm_1.0-9        | tableone_0.13.2 |
| [7] survey_4.2-1       | survival_3.5-5         | Matrix_1.5-4    |
| [10] MASS_7.3-58.3     | marginaleffects_0.12.0 | lmtest_0.9-40   |
| [13] zoo_1.8-12        | knitr_1.42             | ggplot2_3.4.2   |
| [16] data.table_1.14.8 | cobalt_4.5.1           | dplyr_1.1.1     |

loaded via a namespace (and not attached):

|                      |                 |                  |                  |
|----------------------|-----------------|------------------|------------------|
| [1] tidyselect_1.2.0 | xfun_0.39       | mitools_2.4      | splines_4.2.3    |
| [5] haven_2.5.2      | lattice_0.21-8  | labelled_2.11.0  | colorspace_2.1-0 |
| [9] vctrs_0.6.1      | generics_0.1.3  | htmltools_0.5.5  | yaml_2.3.7       |
| [13] utf8_1.2.3      | rlang_1.1.0     | e1071_1.7-13     | pillar_1.9.0     |
| [17] glue_1.6.2      | withr_2.5.0     | DBI_1.1.3        | lifecycle_1.0.3  |
| [21] munsell_0.5.0   | gtable_0.3.3    | codetools_0.2-19 | evaluate_0.21    |
| [25] labeling_0.4.2  | forcats_1.0.0   | fastmap_1.1.1    | class_7.3-22     |
| [29] fansi_1.0.4     | optmatch_0.10.6 | Rcpp_1.0.10      | checkmate_2.2.0  |
| [33] backports_1.4.1 | scales_1.2.1    | jsonlite_1.8.4   | farver_2.1.1     |
| [37] chk_0.8.1       | hms_1.1.3       | digest_0.6.31    | insight_0.19.1   |
| [41] cli_3.6.1       | tools_4.2.3     | magrittr_2.0.3   | proxy_0.4-27     |
| [45] tibble_3.2.1    | crayon_1.5.2    | pkgconfig_2.0.3  | rlemon_0.2.1     |
| [49] rmarkdown_2.21  | rstudioapi_0.14 | R6_2.5.1         | compiler_4.2.3   |

## References

## 4 Effect Modification Analysis within the Propensity score Framework

Mohammad Ehsanul Karim (University of British Columbia)

Observational comparative effectiveness studies often adopt propensity score analysis to adjust for confounding. Although this approach is relatively straightforward to implement, careful thought is needed when treatment effect heterogeneity is present. This chapter illustrates the estimation of subgroup-specific treatment effects using (traditional) covariate adjustment methods, propensity score matching, propensity score weighting, propensity score stratification, and covariate adjustment using propensity scores.

First, we need to install the R package `simcausal`, which can be obtained from GitHub:

```
devtools::install_github('osofr/simcausal', build_vignettes = FALSE)
```

We will use the following data-generation model:

```
require(simcausal)
D <- DAG.empty()
D <- D +
  node("age", distr = "rnorm",
        mean = 2, sd = 4) +
  node("gender", distr = "rbern",
        prob = plogis(4)) +
  node("education", distr = "rbern",
        prob = plogis(3 + 5 * age)) +
  node("diet", distr = "rbern",
        prob = plogis(1 - 3 * education)) +
  node("income", distr = "rbern",
        prob = plogis(2 - 5 * education - 4 * age)) +
  node("smoking", distr = "rbern",
        prob = plogis(1 + 1.2 * gender + 2 * age)) +
  node("hypertension", distr = "rbern",
```

```

    prob = plogis(1 + log(3) * diet +
                  log(1.3) * age +
                  log(3.5) * smoking +
                  log(0.5) * gender))
  Dset <- set.DAG(D)

```

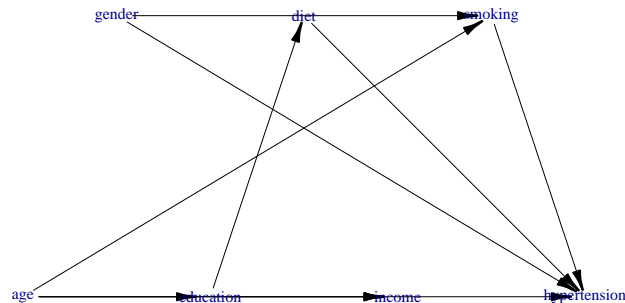
Below is the diagram, with pink lines representing open backdoor path.

using the following vertex attributes:

NAdarkbluenone100.50

using the following edge attributes:

black0.210.60.5



We can now generate an example dataset:

```

Obs.Data <- sim(DAG = Dset, n = 50000, rndseed = 123)
Obs.Data$smoking <- as.character(Obs.Data$smoking)
Obs.Data$income <- as.factor(Obs.Data$income)

```

```
Obs.Data$income <- relevel(Obs.Data$income, ref = "1")
```

Sample data from the hypothetical example of association between hypertension and smoking, where other variables such as income, age [centered], gender, education and diet also plays a role in the data generation process.

|       | age   | gender | education | diet | income | smoking | hypertension |
|-------|-------|--------|-----------|------|--------|---------|--------------|
| 34901 | 12.29 | 1      | 1         | 1    | 0      | 1       | 1            |
| 149   | 10.40 | 1      | 1         | 0    | 0      | 1       | 1            |
| 10060 | 2.99  | 1      | 1         | 0    | 0      | 1       | 0            |
| 22220 | -4.31 | 0      | 0         | 0    | 1      | 0       | 1            |
| 9979  | -6.44 | 0      | 0         | 0    | 1      | 0       | 1            |

## 4.1 Covariate adjustment

### 4.1.1 Interaction approach

Below, we estimate a logistic regression model to assess whether the effect of smoking (the exposure) on hypertension is modified by income levels. This model considers the following variables:

- Outcome: hypertension
- Exposure variables: smoking and income
- Confounders: age and gender

```
require(jtools)

fit.w.em <- glm(hypertension ~ smoking * income + age + gender,
               family = binomial(link = "logit"), data = Obs.Data)

results.model <- summ(fit.w.em, exp = TRUE)
```

Results indicate that the interaction between smoking status and income level is statistically significant ( $p = 0.02$ ).

If we expand previous model to adjust for an additional confounder education, we have:

```
fit.w.int <- glm(hypertension ~ smoking * income + age + gender + education,
               family = binomial(link = "logit"),
               data = Obs.Data)
```

|                  | exp(Est.) | 2.5% | 97.5% | z val. | p    |
|------------------|-----------|------|-------|--------|------|
| (Intercept)      | 5.46      | 4.37 | 6.82  | 14.97  | 0.00 |
| smoking1         | 2.93      | 2.60 | 3.30  | 17.69  | 0.00 |
| income0          | 0.48      | 0.41 | 0.57  | -8.28  | 0.00 |
| age              | 1.29      | 1.27 | 1.31  | 36.77  | 0.00 |
| gender           | 0.54      | 0.43 | 0.67  | -5.55  | 0.00 |
| smoking1:income0 | 1.27      | 1.04 | 1.56  | 2.33   | 0.02 |

```
results.int.model <- summ(fit.w.int, exp = TRUE)
```

|                  | exp(Est.) | 2.5% | 97.5% | z val. | p    |
|------------------|-----------|------|-------|--------|------|
| (Intercept)      | 5.69      | 4.56 | 7.11  | 15.31  | 0.00 |
| smoking1         | 3.35      | 2.95 | 3.79  | 18.85  | 0.00 |
| income0          | 1.09      | 0.85 | 1.40  | 0.68   | 0.49 |
| age              | 1.30      | 1.28 | 1.32  | 37.32  | 0.00 |
| gender           | 0.54      | 0.43 | 0.67  | -5.58  | 0.00 |
| education        | 0.42      | 0.35 | 0.51  | -8.87  | 0.00 |
| smoking1:income0 | 1.10      | 0.90 | 1.35  | 0.93   | 0.35 |

The interaction term between income and smoking is no longer statistically significant ( $p = 0.35$ ).

We can generate a summary report from aforementioned effect modification analysis.

```
require(interactionR)

em.object <- interactionR(fit.w.em,
                          exposure_names = c("income0", "smoking1"),
                          ci.type = "mover", ci.level = 0.95,
                          em = TRUE, recode = FALSE)
```

The table below depicts the adjusted odds ratios for income levels ( $\text{high} = 0$ , and  $\text{low} = 1$ ). The variables  $\text{CI.l1}$  and  $\text{CI.u1}$  depict the lower and upper limits of the 95 percent confidence intervals,  $\text{OR11} = OR_{A=1, M=1}$ ,  $\text{OR10} = OR_{A=1}$ ,  $\text{OR01} = OR_{M=1}$  and  $\text{OR00}$  captures the reference.

Similarly, for the analysis adjusting for an additional confounder **education**, we have:

Table 4.1: Summary report from an interaction analysis when investigating association between two exposure variables (smoking and income) and hypertension.

| Measures                             | Estimates | CI.ll | CI.ul |
|--------------------------------------|-----------|-------|-------|
| OR00                                 | 1.00      | NA    | NA    |
| OR01                                 | 2.93      | 2.60  | 3.30  |
| OR10                                 | 0.48      | 0.41  | 0.57  |
| OR11                                 | 1.80      | 1.63  | 1.98  |
| OR(smoking1 on outcome [income0==0]) | 2.93      | 2.60  | 3.30  |
| OR(smoking1 on outcome [income0==1]) | 3.72      | 3.14  | 4.41  |
| Multiplicative scale                 | 1.27      | 1.04  | 1.56  |
| RERI                                 | -0.61     | -0.98 | -0.29 |

Table 4.2: Summary report from an interaction analysis when investigating association between two exposure variables (smoking and income) and hypertension.

| Measures                             | Estimates | CI.ll | CI.ul |
|--------------------------------------|-----------|-------|-------|
| OR00                                 | 1.00      | NA    | NA    |
| OR01                                 | 1.09      | 0.85  | 1.40  |
| OR10                                 | 3.35      | 2.95  | 3.79  |
| OR11                                 | 4.02      | 3.29  | 4.92  |
| OR(income0 on outcome [smoking1==0]) | 1.09      | 0.85  | 1.40  |
| OR(income0 on outcome [smoking1==1]) | 1.20      | 1.00  | 1.45  |
| OR(smoking1 on outcome [income0==0]) | 3.35      | 2.95  | 3.79  |
| OR(smoking1 on outcome [income0==1]) | 3.69      | 3.11  | 4.37  |
| Multiplicative scale                 | 1.10      | 0.90  | 1.35  |
| RERI                                 | 0.59      | 0.03  | 1.27  |
| AP                                   | 0.15      | 0.00  | 0.26  |
| SI                                   | 1.24      | 1.01  | 1.53  |

```
# test run with additive model
Obs.Data$smoking <- as.numeric(as.character(Obs.Data$smoking))
Obs.Data$income <- as.numeric(as.character(Obs.Data$income))
fit.w.int.add <- glm(hypertension ~ smoking * income + age + gender + education,
                     family = gaussian(link = "identity"), data = Obs.Data)
sim_slopes(fit.w.int.add, pred = smoking, modx = income,
            exp = TRUE, robust = TRUE,
            confint = TRUE, data = Obs.Dat)
```

## JOHNSON-NEYMAN INTERVAL

When income is INSIDE the interval  $[-3.27, 16.87]$ , the slope of smoking is  $p < .05$ .

Note: The range of observed values of income is  $[0.00, 1.00]$

## SIMPLE SLOPES ANALYSIS

Slope of smoking when income = 0.00 (0):

| Est. | S.E. | 2.5% | 97.5% | t val. | p    |
|------|------|------|-------|--------|------|
| 0.25 | 0.02 | 1.24 | 1.34  | 12.76  | 0.00 |

Slope of smoking when income = 1.00 (1):

| Est. | S.E. | 2.5% | 97.5% | t val. | p    |
|------|------|------|-------|--------|------|
| 0.28 | 0.01 | 1.30 | 1.34  | 34.53  | 0.00 |

## 4.1.2 Stratification

This approach involves estimating a regression model in different strata of the discrete effect modifier income:

```
# Estimate the prognostic effect of smoking in low income individuals
fit.income1 <- glm(hypertension ~ smoking + age + gender,
  family = binomial(link = "logit"),
  data = subset(Obs.Data, income == 1))

# Estimate the prognostic effect of smoking in high income individuals
fit.income0 <- glm(hypertension ~ smoking + age + gender,
  family = binomial(link = "logit"),
  data = subset(Obs.Data, income == 0))
```

The table below summarizes the adjusted odds ratios for smoking across the different income levels (**low** = 1, and **high** = 0) as obtained using the stratified approach.

Note that we can obtain the same results by estimating a regression model with an interaction term between the modifier and all covariates:

| Value of income | Estimate | 2.5 % | 97.5 % | z value | p value |
|-----------------|----------|-------|--------|---------|---------|
| 1               | 3.07     | 2.71  | 3.47   | 17.65   | 0       |
| 0               | 3.59     | 3.02  | 4.26   | 14.57   | 0       |

```
fit.all.int <- glm(hypertension ~ income * (smoking + age + gender),
                  family = binomial(link = "logit"), data = Obs.Data)

# Odds ratio for smoking in individuals with low income
exp(coef(fit.all.int)["smoking"])
```

```
smoking
3.59026
```

```
# Odds ratio for smoking in individuals with high income
exp(coef(fit.all.int)["smoking"] + coef(fit.all.int)["income:smoking"])
```

```
smoking
3.066878
```

## 4.2 Propensity score matching

### 4.2.1 Stratification with exact matching within subgroups

We simulate another example dataset using aforementioned DAG, but restrict the sample size to 5000 individuals to reduce computational burden.

```
set.seed(123)
Obs.Data <- sim(DAG = Dset, n = 5000, rndseed = 123)
```

We first estimate the propensity of smoking in the high-income group (`income == 0`):

```
require(MatchIt)

match.income.0 <- matchit(smoking ~ age + gender,
                          data = subset(Obs.Data, income == 0),
                          method = "full", distance = "glm", link = "logit")
data.income.0 <- match.data(match.income.0)
```



Below, we draw a sample from the high-income group based on the hypothetical example of an association between hypertension and smoking. Here age [centered], gender, education, and diet are covariates.

|      | age        | gender | education | diet | income | smoking | hypertension | distance  |
|------|------------|--------|-----------|------|--------|---------|--------------|-----------|
| 657  | 6.0810120  | 0      | 1         | 1    | 0      | 1       | 1            | 0.9999874 |
| 4932 | 1.6109860  | 1      | 1         | 0    | 0      | 1       | 0            | 0.9943155 |
| 252  | -0.2475055 | 1      | 1         | 1    | 0      | 0       | 1            | 0.8525107 |
| 2693 | -0.2511048 | 1      | 1         | 0    | 0      | 1       | 1            | 0.8516785 |
| 1646 | -0.2836155 | 1      | 0         | 1    | 0      | 1       | 1            | 0.8439843 |

|      | weights    | subclass |
|------|------------|----------|
| 657  | 1.00000000 | 36       |
| 4932 | 1.00000000 | 50       |
| 252  | 0.03296089 | 25       |
| 2693 | 1.00000000 | 25       |
| 1646 | 1.00000000 | 4        |

Now, we do the same for the low-income group (`income == 1`):

```
match.income.1 <- matchit(smoking ~ age + gender,
                          data = subset(Obs.Data, income == 1),
                          method = "full", distance = "glm", link = "logit")
data.income.1 <- match.data(match.income.1)
```

We estimated the exposure effect from a weighted outcome model for the matched data. While the `weights` are essential for estimating the point estimate from the outcome model, the `subclass` variable assists in calculating the robust variance of the exposure effect estimate.

```
# Treatment effect estimation
fit.income.0 <- glm(hypertension ~ smoking + age + gender,
                   data = data.income.0, weights = weights,
                   family = binomial("logit"))
fit.income.1 <- glm(hypertension ~ smoking + age + gender,
                   data = data.income.1, weights = weights,
                   family = binomial("logit"))

# Robust variance calculation
fit.nexp.adj.res1 <- summ(fit.income.1,
                        robust = TRUE,
                        cluster = "subclass",
                        confint = TRUE)
fit.nexp.adj.res0 <- summ(fit.income.0,
                        robust = TRUE,
```

```
cluster = "subclass",
confint = TRUE)
```

Table 4.3: Subgroup-specific treatment effect estimates (expressed in log-OR) from the hypothetical example using the stratified approach.

| Value of income | Est. | 2.5%   | 97.5% | z val. | p    |
|-----------------|------|--------|-------|--------|------|
| 0               | 3.74 | -37.58 | 45.06 | 0.18   | 0.86 |
| 1               | 1.39 | 0.94   | 1.85  | 6.04   | 0.00 |

#### 4.2.2 Joint approach without exact matching within subgroups

Here, entire cohort data is used to estimate the propensity scores, and the effect modifier income is considered as a covariate in the propensity score model:

```
ps.formula <- as.formula("smoking ~ age + gender + income")
match.obj.j <- matchit(ps.formula, data = Obs.Data,
                      method = "full",
                      distance = "glm",
                      link = "logit")
match.data.j <- match.data(match.obj.j)

fit.joint.no.exact <- glm(hypertension ~ smoking*income + age + gender,
                        data = match.data.j,
                        weights = weights,
                        family = binomial("logit"))

require(interactions)
nem.nexp.adj.res <- sim_slopes(fit.joint.no.exact,
                              pred = smoking,
                              modx = income,
                              robust = "HC1",
                              cluster = "subclass",
                              johnson_neyman = TRUE,
                              confint = TRUE,
                              data = match.data.j)
```

#### 4.2.3 Joint approach with exact matching within subgroups

We specify the moderator variable's name in the `exact` argument of the `matchit` function.

Table 4.4: Subgroup-specific treatment effect estimates (expressed in log-OR) from the hypothetical example using the joint approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 3.85 | 1.00 | 1.89 | 5.82  | 3.84   | 0 |
| 1               | 1.40 | 0.28 | 0.85 | 1.95  | 4.99   | 0 |

```
ps.formula.no.mod <- as.formula("smoking ~ age + gender")
match.obj.js <- matchit(ps.formula.no.mod, data = Obs.Data,
                        method = "full", distance = "glm", link = "logit",
                        exact = "income")
match.data.js <- match.data(match.obj.js)
fit.joint.exact <- glm(hypertension ~ smoking*income + age + gender,
                      data = match.data.js, weights = weights,
                      family = binomial("logit"))
js.nexp.adj.res <- sim_slopes(fit.joint.exact,
                             pred = smoking, modx = income,
                             robust = "HC1", cluster = "subclass",
                             johnson_neyman = FALSE, confint = TRUE,
                             data = match.data.js)
```

Table 4.5: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the Joint model, separate matching approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 3.89 | 1.01 | 1.92 | 5.87  | 3.87   | 0 |
| 1               | 1.38 | 0.28 | 0.84 | 1.93  | 4.95   | 0 |

#### 4.2.4 Interaction approach without exact matching within subgroups

Analysts incorporate relevant moderator-covariate interactions into the propensity score model that align with biological plausibility. For instance, in the case study we considered an interaction between age (a covariate) and income (a moderator), but did not include other interactions terms.

```
ps.formula.with.int <- formula("smoking ~ age*income + gender")
match.obj.i <- matchit(ps.formula.with.int, data = Obs.Data,
                      method = "full", distance = "glm", link = "logit")
match.data.i <- match.data(match.obj.i)
```

```

fit.int.no.exact <- glm(hypertension ~ smoking*income + age + gender,
                        data = match.data.i, weights = weights,
                        family = binomial("logit"))
i.nexp.adj.res <- sim_slopes(fit.int.no.exact,
                             pred = smoking, modx = income,
                             robust = "HC1", cluster = "subclass",
                             johnson_neyman = FALSE, confint = TRUE,
                             data = match.data.i)

```

Table 4.6: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the interaction approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 3.87 | 1.00 | 1.90 | 5.83  | 3.86   | 0 |
| 1               | 1.39 | 0.28 | 0.84 | 1.94  | 4.95   | 0 |

## 4.2.5 Interaction approach with exact matching within subgroups

This method bears resemblance to the interaction approach for propensity score estimation. However, when it comes to matching, researchers match within each moderator subgroup.

```

match.obj.is <- matchit(ps.formula.with.int, data = Obs.Data,
                        method = "full", distance = "glm", link = "logit",
                        exact = "income")
match.data.is <- match.data(match.obj.is)
fit.int.exact <- glm(hypertension ~ smoking*income + age + gender,
                     data = match.data.is, weights = weights,
                     family = binomial("logit"))
is.nexp.adj.res <- sim_slopes(fit.int.exact,
                             pred = smoking, modx = income,
                             robust = "HC1", cluster = "subclass",
                             johnson_neyman = FALSE, confint = TRUE,
                             data = match.data.is)

```

## 4.3 Propensity Score Weighting

### 4.3.1 Common model

This approach adds confounder-moderator interactions in the common weight model.

Table 4.7: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the interaction model, separate matching approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 3.86 | 1.00 | 1.90 | 5.83  | 3.85   | 0 |
| 1               | 1.40 | 0.28 | 0.85 | 1.95  | 4.99   | 0 |

```
require(WeightIt)
W.out <- weightit(ps.formula.with.int,
                  data = Obs.Data,
                  method = "ps",
                  estimand = "ATT")

require(survey)
d.w <- svydesign(~1, weights = W.out$weights, data = Obs.Data)
fit2w <- svyglm(hypertension ~ smoking*income, design = d.w,
                family = binomial("logit"))
w.nexp.adj.res <- sim_slopes(fit2w, pred = smoking, modx = income,
                             confint = TRUE)
```

Table 4.8: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the weighting approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | t val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 2.66 | 0.63 | 1.42 | 3.89  | 4.23   | 0 |
| 1               | 1.32 | 0.25 | 0.83 | 1.82  | 5.24   | 0 |

We can adjust previous analysis model to adopt stabilized weights for the propensity score (`stabilize = TRUE`):

```
W.out.st <- weightit(ps.formula.with.int, data = Obs.Data,
                    method = "ps",
                    estimand = "ATT",
                    stabilize = TRUE)

d.sw <- svydesign(~1, weights = W.out.st$weights, data = Obs.Data)
fit2sw <- svyglm(hypertension ~ smoking*income + age + gender,
                 design = d.sw,
                 family = binomial("logit"))
ws.nexp.adj.res <- sim_slopes(fit2sw,
                              pred = smoking, modx = income,
                              confint = TRUE)
```

Table 4.9: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using stabilized propensity score weights.

| Value of income | Est. | S.E. | 2.5% | 97.5% | t val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 2.27 | 0.73 | 0.84 | 3.69  | 3.12   | 0 |
| 1               | 1.32 | 0.25 | 0.83 | 1.82  | 5.23   | 0 |

### 4.3.2 Separate models

Propensity score weighting approach with weights estimated separately from each subgroup:

```
ps.formula.with.no.int <- formula("smoking ~ age + gender")
W.out1 <- weightit(ps.formula.with.no.int,
                  data = subset(Obs.Data, income == 1),
                  method = "ps",
                  estimand = "ATT")
trimmed.weight.1.percent1 <- trim(W.out1$weights,
                                  at = 1, lower = TRUE)
```

Table 4.10: Weight summaries before and after truncation.

| Weight               | Min. | 1st Qu. | Median | Mean | 3rd Qu. | Max.  |
|----------------------|------|---------|--------|------|---------|-------|
| Raw weights          | 0    | 0.01    | 0.11   | 0.45 | 1       | 11.69 |
| 1% truncated weights | 0    | 0.01    | 0.11   | 0.44 | 1       | 7.61  |

```
# Outcome model for income = 1
d.w1 <- svydesign(~1, weights = trimmed.weight.1.percent1,
                data = subset(Obs.Data, income == 1))
fit2unadj1 <- svyglm(hypertension ~ smoking, design = d.w1,
                    family = binomial("logit"))

# weight model for income = 0
W.out0 <- weightit(ps.formula, data = subset(Obs.Data, income == 0),
                  method = "ps", estimand = "ATT")
trimmed.weight.1.percent0 <- trim(W.out0$weights, at = 1, lower = TRUE)

# Outcome model for income = 0
d.w0 <- svydesign(~1, weights = trimmed.weight.1.percent0,
                data = subset(Obs.Data, income == 0))
fit2unadj0 <- svyglm(hypertension ~ smoking, design = d.w0,
```

```

family = binomial("logit"))

fit.exp.adj.res1 <- summ(fit2unadj1, confint = TRUE)
fit.exp.adj.res0 <- summ(fit2unadj0, confint = TRUE)

```

Table 4.11: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the propensity score weighting approach (Separate weight models).

| Value of income | Est. | 2.5% | 97.5% | t val. | p |
|-----------------|------|------|-------|--------|---|
| 0               | 2.21 | 1.27 | 3.15  | 4.60   | 0 |
| 1               | 1.34 | 0.85 | 1.83  | 5.36   | 0 |

### 4.3.3 Weights from the subgroup balancing propensity scores

Subgroup balancing propensity scores for propensity score weighting:

```

w.out <- weightit(smoking ~ age + gender + income,
                  data = Obs.Data,
                  method = "ps", estimand = "ATT")
w.out.sb <- sbps(w.out, moderator = "income")
d.w.sb <- svydesign(~1, weights = w.out.sb$weights, data = Obs.Data)
fit2unadj.sb <- svyglm(hypertension ~ smoking*income, design = d.w.sb,
                      family = binomial("logit"))
sb.w.nexp.adj.res <- sim_slopes(fit2unadj.sb,
                                pred = smoking,
                                modx = income,
                                confint = TRUE,
                                johnson_neyman = FALSE,)

```

Table 4.12: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using the subgroup balancing weighting approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | t val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 2.68 | 0.64 | 1.44 | 3.92  | 4.22   | 0 |
| 1               | 1.32 | 0.25 | 0.82 | 1.82  | 5.22   | 0 |

## 4.4 Covariate adjustment for the propensity score

### 4.4.1 As continuous covariate

An implementation of propensity scores as a continuous covariate in the outcome model:

```
# Separate models for each subgroup

# For subgroup income = 1
Obs.Data$ps[Obs.Data$income == 1] <- glm(ps.formula,
                                         data = subset(Obs.Data, income == 1),
                                         family = "binomial")$fitted.values
fit2adj1 <- glm(hypertension ~ smoking + age + gender,
               family = binomial("logit"),
               data = subset(Obs.Data, income == 1))

# For subgroup income = 0
Obs.Data$ps[Obs.Data$income == 0] <- glm(ps.formula,
                                         data = subset(Obs.Data, income == 0),
                                         family = "binomial")$fitted.values
fit2adj0 <- glm(hypertension ~ smoking + age + gender,
               family = binomial("logit"),
               data = subset(Obs.Data, income == 0))

fit.nexp.adj.res1 <- summ(fit2adj1, robust = TRUE, confint = TRUE)
fit.nexp.adj.res0 <- summ(fit2adj0, robust = TRUE, confint = TRUE)
```

Table 4.13: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using Propensity Score as a covariate adjustment approach (considering separate models for each subgroup).

| Value of income | Est. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|-------|--------|---|
| 0               | 1.16 | 0.56 | 1.75  | 3.83   | 0 |
| 1               | 1.37 | 0.96 | 1.77  | 6.61   | 0 |

```
# Common model
Obs.Data$ps <- glm(ps.formula.with.int, data = Obs.Data,
                  family = "binomial")$fitted.values
```

Warning: glm.fit: fitted probabilities numerically 0 or 1 occurred



```

fit2adjc <- glm(hypertension ~ smoking*income + age + gender + ps,
               family = binomial("logit"),
               data = Obs.Data)
c.nexp.adj.res <- sim_slopes(fit2adjc,
                           pred = smoking, modx = income,
                           confint = TRUE,
                           data = Obs.Data)

```

Table 4.14: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using Propensity Score as a covariate adjustment approach (considering a common model).

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 1.17 | 0.29 | 0.61 | 1.74  | 4.07   | 0 |
| 1               | 1.43 | 0.23 | 0.98 | 1.87  | 6.30   | 0 |

#### 4.4.2 As quantiles

The propensity scores as a categorical covariate, broken by quintiles, in the outcome model.

```

Obs.Data$ps <- glm(ps.formula.with.int,
                  data = Obs.Data,
                  family = "binomial")$fitted.values
quintiles <- quantile(Obs.Data$ps,
                     prob = seq(from = 0, to = 1, by = 0.2),
                     na.rm = T)
Obs.Data$psq <- cut(Obs.Data$ps, breaks = quintiles,
                  labels = seq(1,5), include.lowest = T)
Obs.Data$psq <- as.factor(Obs.Data$psq)

fit2adjq <- glm(hypertension ~ (smoking*psq)*income,
               family = binomial("logit"),
               data = Obs.Data)
cq.nexp.adj.res <- sim_slopes(fit2adjq,
                           pred = smoking,
                           modx = income,
                           confint = TRUE,
                           data = Obs.Data)

```

Table 4.15: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using Propensity Score as a covariate adjustment approach (as quintiles).

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 3.08 | 0.63 | 1.85 | 4.32  | 4.91   | 0 |
| 1               | 2.60 | 0.47 | 1.68 | 3.51  | 5.56   | 0 |

## 4.5 Propensity Score Stratification

Here is an implementation of propensity score stratification approach by using the marginal mean weighting through stratification (MMWS):

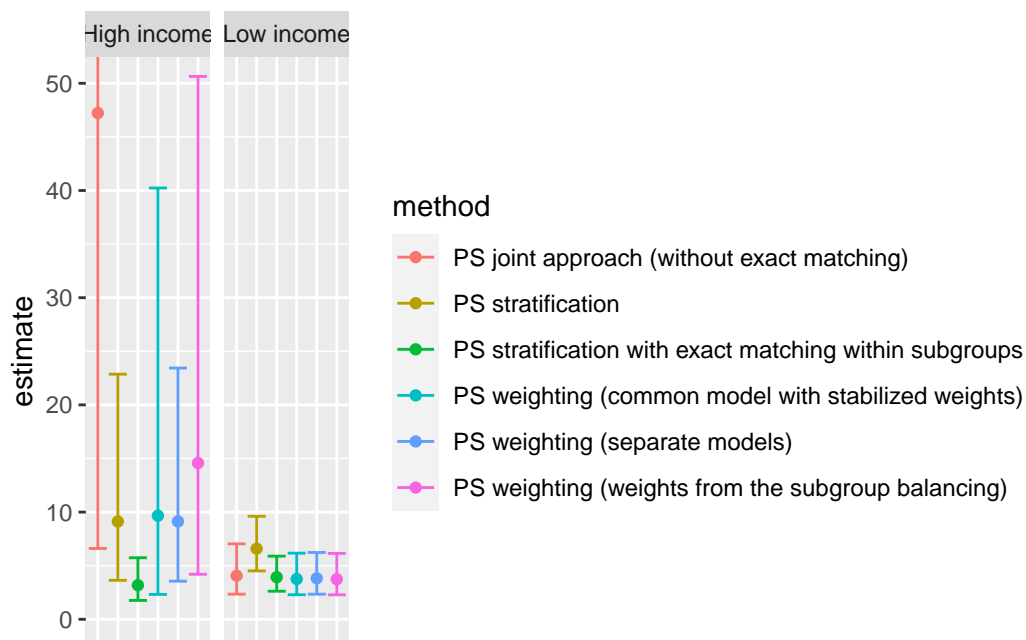
```
match.obj <- matchit(ps.formula, data = Obs.Data,
                    method = "subclass", subclass = 3,
                    estimand = "ATT", min.n = 10)
data.subclass <- match.data(match.obj)
subclass.fit <- glm(hypertension ~ smoking*income, family = binomial("logit"),
                  data = data.subclass,
                  weights = weights)
subclass.nexp.adj.res <- sim_slopes(subclass.fit,
                                   pred = smoking,
                                   modx = income,
                                   confint = TRUE,
                                   robust = "HC3",
                                   johnson_neyman = FALSE,
                                   data = data.subclass)
```

Table 4.16: Subgroup-specific exposure effect estimates (expressed in log-OR) from the hypothetical example using propensity score stratification approach.

| Value of income | Est. | S.E. | 2.5% | 97.5% | z val. | p |
|-----------------|------|------|------|-------|--------|---|
| 0               | 2.21 | 0.47 | 1.29 | 3.13  | 4.71   | 0 |
| 1               | 1.89 | 0.19 | 1.51 | 2.26  | 9.78   | 0 |

## 4.6 Summary

The marginal odds ratios for `smoking` are summarized below



## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19045)
```

```
Matrix products: default
```

```
locale:
```

```
[1] LC_COLLATE=Dutch_Netherlands.utf8 LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

```
attached base packages:
```

```
[1] grid      stats      graphics  grDevices  utils      datasets  methods
[8] base
```

```
other attached packages:
```

```
[1] scales_1.2.1      ggplot2_3.4.2      readstata13_0.10.1 interactions_1.1.5
```

|      |                    |                  |                 |               |
|------|--------------------|------------------|-----------------|---------------|
| [5]  | interactionR_0.1.6 | jtools_2.2.1     | simcausal_0.5.6 | xtable_1.8-4  |
| [9]  | dplyr_1.1.1        | kableExtra_1.3.4 | knitr_1.42      | cowplot_1.1.1 |
| [13] | survey_4.2-1       | survival_3.5-5   | Matrix_1.5-4    | broom_1.0.4   |
| [17] | MatchIt_4.5.3      | sandwich_3.0-2   | lmtest_0.9-40   | zoo_1.8-12    |
| [21] | optmatch_0.10.6    | WeightIt_0.14.1  | cobalt_4.5.1    | table1_1.4.3  |

loaded via a namespace (and not attached):

|      |                  |                      |                         |
|------|------------------|----------------------|-------------------------|
| [1]  | fontquiver_0.2.1 | webshot_0.5.4        | httr_1.4.6              |
| [4]  | tools_4.2.3      | backports_1.4.1      | utf8_1.2.3              |
| [7]  | R6_2.5.1         | DBI_1.1.3            | colorspace_2.1-0        |
| [10] | withr_2.5.0      | tidyselect_1.2.0     | curl_5.0.0              |
| [13] | compiler_4.2.3   | textshaping_0.3.6    | cli_3.6.1               |
| [16] | rvest_1.0.3      | expm_0.999-7         | flextable_0.9.1         |
| [19] | xml2_1.3.3       | officer_0.6.2        | fontBitstreamVera_0.1.1 |
| [22] | mvtnorm_1.1-3    | askpass_1.1          | systemfonts_1.0.4       |
| [25] | stringr_1.5.0    | digest_0.6.31        | rmarkdown_2.21          |
| [28] | svglite_2.1.1    | gfonts_0.2.0         | pkgconfig_2.0.3         |
| [31] | htmltools_0.5.5  | fastmap_1.1.1        | rlang_1.1.0             |
| [34] | rstudioapi_0.14  | httpcode_0.3.0       | shiny_1.7.4             |
| [37] | generics_0.1.3   | jsonlite_1.8.4       | car_3.1-2               |
| [40] | zip_2.3.0        | magrittr_2.0.3       | Formula_1.2-5           |
| [43] | Rcpp_1.0.10      | munsell_0.5.0        | fansi_1.0.4             |
| [46] | abind_1.4-5      | gdtools_0.3.3        | lifecycle_1.0.3         |
| [49] | stringi_1.7.12   | yaml_2.3.7           | carData_3.0-5           |
| [52] | promises_1.2.0.1 | crayon_1.5.2         | lattice_0.21-8          |
| [55] | splines_4.2.3    | pander_0.6.5         | pillar_1.9.0            |
| [58] | uuid_1.1-0       | igraph_1.4.2         | crul_1.4.0              |
| [61] | glue_1.6.2       | evaluate_0.21        | msm_1.7                 |
| [64] | mitools_2.4      | fontLiberation_0.1.0 | data.table_1.14.8       |
| [67] | vctrs_0.6.1      | httpuv_1.6.9         | gtable_0.3.3            |
| [70] | openssl_2.0.6    | purrr_1.0.1          | tidyr_1.3.0             |
| [73] | assertthat_0.2.1 | xfun_0.39            | mime_0.12               |
| [76] | later_1.3.0      | ragg_1.2.5           | viridisLite_0.4.2       |
| [79] | tibble_3.2.1     | ellipsis_0.3.2       |                         |

## 5 Dealing with missing data

Johanna Munoz (Julius Center for Health Sciences and Primary Care)  
Thomas Debray (Smart Data Analysis and Statistics B.V.)

In this example, we consider the estimation of comparative treatment effects in the absence of treatment-effect heterogeneity.

### 5.0.1 Prepare R environment

```
library(mice)
library(dplyr)
library(ggmice)
library(MatchThem)
```

### 5.0.2 Generating an observational dataset

We can simulate an observational dataset of  $N = 3000$  patients as follows:

```
data_noHTE <- generate_data(n = 3000, seed = 1234)
```

This dataset does not (yet) contain any missing values;

The simulated dataset contains two treatment groups with differences in baseline characteristics. For example, the figure below shows that we have baseline imbalance in age.

### 5.0.3 Generating missing values

Missing values can be generated using the function `getmissdata()`, which considers the following patterns of missingness for the previous number of relapses (`prerelapse_num`):

1. MAR: missingness depends on **age** and **sex**

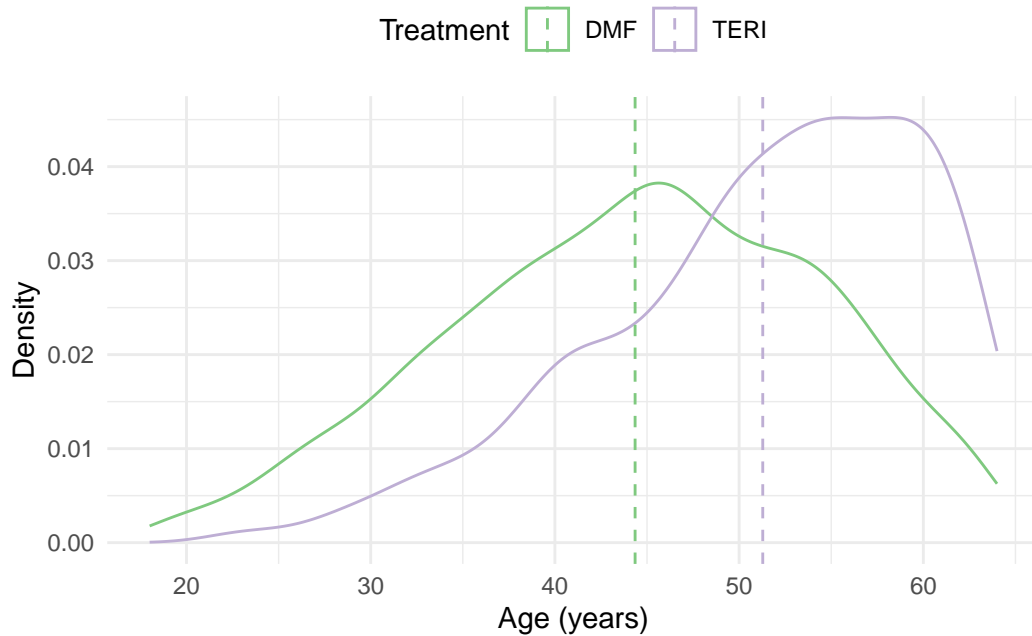


Figure 5.1: Distribution of the EDSS score at each time point

2. MART: missingness depends on `age`, `sex` and the treatment variable `treatment`
3. MARTY: missingness depends on `age`, `sex`, `treatment` and the outcome variable `y`
4. MNAR: missingness depends on `age`, `sex` and `prerelapse_num`

```
mdata_noHTE <- getmissdata(data_noHTE, "MART")
```

After introducing missing values, we only have complete data for  $N = 946$  patients.

## 5.1 Analysis of incomplete data

### 5.1.1 Complete Case Analysis

Below, we describe how to estimate the ATE using propensity score matching.

```
impdata <- mdata_noHTE[complete.cases(mdata_noHTE), ]

# Apply Matching
mout <- matchit(DMF ~ age + female + prevDMTefficacy + premedicalcost + prerelapse_num,
               data = impdata,
```

Table 5.1: Baseline characteristics of the incomplete dataset.

|                                 | DMF                | TERI                | Overall            |
|---------------------------------|--------------------|---------------------|--------------------|
|                                 | (N=2265)           | (N=735)             | (N=3000)           |
| <b>Age (years)</b>              |                    |                     |                    |
| Mean (SD)                       | 44.4 (10.0)        | 51.3 (8.72)         | 46.2 (10.1)        |
| Median [Min, Max]               | 45.0 [18.0, 64.0]  | 53.0 [23.0, 64.0]   | 47.0 [18.0, 64.0]  |
| Missing                         | 248 (10.9%)        | 57 (7.8%)           | 305 (10.2%)        |
| <b>Female Sex</b>               |                    |                     |                    |
| Yes                             | 1740 (76.8%)       | 526 (71.6%)         | 2266 (75.5%)       |
| No                              | 525 (23.2%)        | 209 (28.4%)         | 734 (24.5%)        |
| <b>Efficacy of previous DMT</b> |                    |                     |                    |
| None                            | 740 (32.7%)        | 325 (44.2%)         | 1065 (35.5%)       |
| Low                             | 190 (8.4%)         | 59 (8.0%)           | 249 (8.3%)         |
| Medium or High                  | 830 (36.6%)        | 246 (33.5%)         | 1076 (35.9%)       |
| Missing                         | 505 (22.3%)        | 105 (14.3%)         | 610 (20.3%)        |
| <b>Prior medical costs</b>      |                    |                     |                    |
| Mean (SD)                       | 9970 (10700)       | 25500 (35400)       | 13900 (21200)      |
| Median [Min, Max]               | 6530 [164, 102000] | 12500 [259, 337000] | 7450 [164, 337000] |
| Missing                         | 257 (11.3%)        | 52 (7.1%)           | 309 (10.3%)        |
| <b>Number of prior symptoms</b> |                    |                     |                    |
| 0                               | 157 (6.9%)         | 58 (7.9%)           | 215 (7.2%)         |
| 1                               | 1169 (51.6%)       | 411 (55.9%)         | 1580 (52.7%)       |
| >=2                             | 435 (19.2%)        | 159 (21.6%)         | 594 (19.8%)        |
| Missing                         | 504 (22.3%)        | 107 (14.6%)         | 611 (20.4%)        |
| <b>Number of prior relapses</b> |                    |                     |                    |
| Mean (SD)                       | 0.453 (0.671)      | 0.408 (0.646)       | 0.436 (0.662)      |
| Median [Min, Max]               | 0 [0, 4.00]        | 0 [0, 3.00]         | 0 [0, 4.00]        |
| Missing                         | 1365 (60.3%)       | 152 (20.7%)         | 1517 (50.6%)       |

```

        family = binomial,
        method = "full",
        caliper = 0.2,
        estimand = "ATE",
        replace = FALSE)

mdata <- as.data.table(match.data(mout))
match_mod <- glm("y ~ DMF + offset(log(years))",
                family = poisson(link = "log"),
                data = mdata,
                weights = weights)

# Estimate robust variance-covariance matrix
tx_var <- vcovCL(match_mod, cluster = ~ subclass, sandwich = TRUE)

```

We can extract the treatment effect estimate as follows:

```

# Treatment effect estimate (log rate ratio)
coef(match_mod)["DMF"]

```

```

      DMF
-0.3685717

```

```

# Standard error
sqrt(tx_var["DMF", "DMF"])

```

```
[1] 0.1521243
```

### 5.1.2 Multiple Imputation (within method)

In this approach, we will generate  $m = 5$  imputed datasets and perform matching within each imputed dataset. We first need to specify how the variables `prevDMTefficacy`, `premedicalcost`, `numSymptoms`, `prerelapse_num` and `age` will be imputed:

```

# We add a covariate for log(years)
impdata <- mdata_noHTE %>% mutate(logyears = log(years))

# Specify the conditional imputation models
form_y <- list(prevDMTefficacy ~ age + female + logyears + premedicalcost + numSymptoms +
               treatment + prerelapse_num + y,

```



```

premedicalcost ~ age + female + logyears + prevDMTefficacy + numSymptoms +
  treatment + prerelapse_num + y,
numSymptoms ~ age + female + premedicalcost + logyears + prevDMTefficacy +
  prerelapse_num + treatment + y,
prerelapse_num ~ age + female + premedicalcost + logyears + prevDMTefficacy
  numSymptoms + treatment + y,
age ~ prerelapse_num + female + premedicalcost + logyears + prevDMTefficacy
  numSymptoms + treatment + y)
form_y <- name.formulas(form_y)

# Adopt predictive mean matching for imputing the incomplete variables
imp0 <- mice(impdata, form = form_y, maxit = 0)
method <- imp0$method
method["numSymptoms"] <- "pmm"
method["prevDMTefficacy"] <- "pmm"

# Generate 5 imputed datasets
imp <- mice(impdata, form = form_y, method = method, m = 5, maxit = 100)

```

We can now estimate the ATE using propensity score analysis in each of the imputed datasets. We here adopt full matching without replacement.

```

# Matching based on PS model
mout <- matchthem(DMF ~ age + female + prevDMTefficacy + premedicalcost + prerelapse_num,
  datasets = imp,
  approach = "within",
  method = "full",
  caliper = 0.2,
  family = binomial,
  estimand = "ATE",
  distance = "glm",
  link = "logit",
  replace = FALSE)

```

The results are then combined using Rubin's rules. We adopt robust standard errors to account for clustering of matched individuals.

```

match_mod <- summary(pool(with(mout, svyglm(y ~ DMF + offset(log(years)),
  family = poisson(link = "log")),
  cluster = TRUE)), conf.int = TRUE)

```

We can extract the treatment effect estimate and corresponding standard error as follows:

```
# Treatment effect estimate (log rate ratio)
(match_mod %>% filter(term == "DMF"))$estimate
```

```
[1] -0.1554094
```

```
# Standard error
(match_mod %>% filter(term == "DMF"))$std.error
```

```
[1] 0.2202132
```

### 5.1.3 Multiple Imputation (across method)

```
# Matching based on PS model
mout <- matchthem(DMF ~ age + female + prevDMTefficacy + premedicalcost + prerelapse_num,
  datasets = imp,
  approach = "across",
  method = "full",
  caliper = 0.2,
  family = binomial,
  estimand = "ATE",
  distance = "glm",
  link = "logit",
  replace = FALSE)
```

The results are then combined using Rubin's rules. We adopt robust standard errors to account for clustering of matched individuals.

```
match_mod <- summary(pool(with(mout, svyglm(y ~ DMF + offset(log(years)),
  family = poisson(link = "log")),
  cluster = TRUE)), conf.int = TRUE)
```

We can extract the treatment effect estimate and corresponding standard error as follows:

```
# Treatment effect estimate (log rate ratio)
(match_mod %>% filter(term == "DMF"))$estimate
```

```
[1] -0.3461563
```

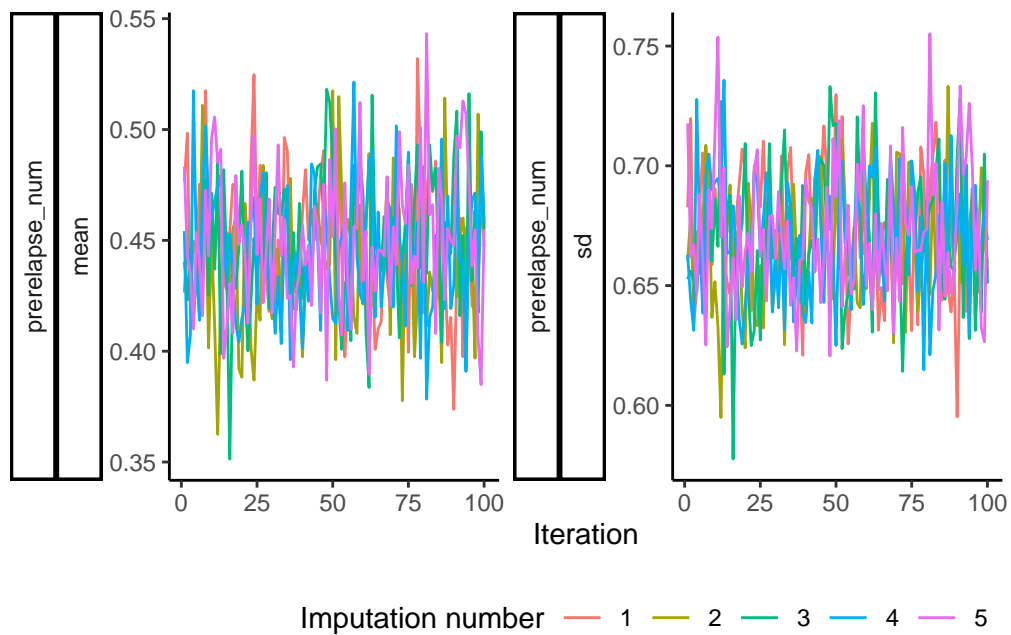
```
# Standard error
(match_mod %>% filter(term == "DMF"))$std.error
```

```
[1] 0.1351187
```

## 5.2 Convergence checking

We can inspect convergence for the imputed variable `prerelapse_num` using a trace plot:

```
plot_trace(imp, vrb = "prerelapse_num")
```

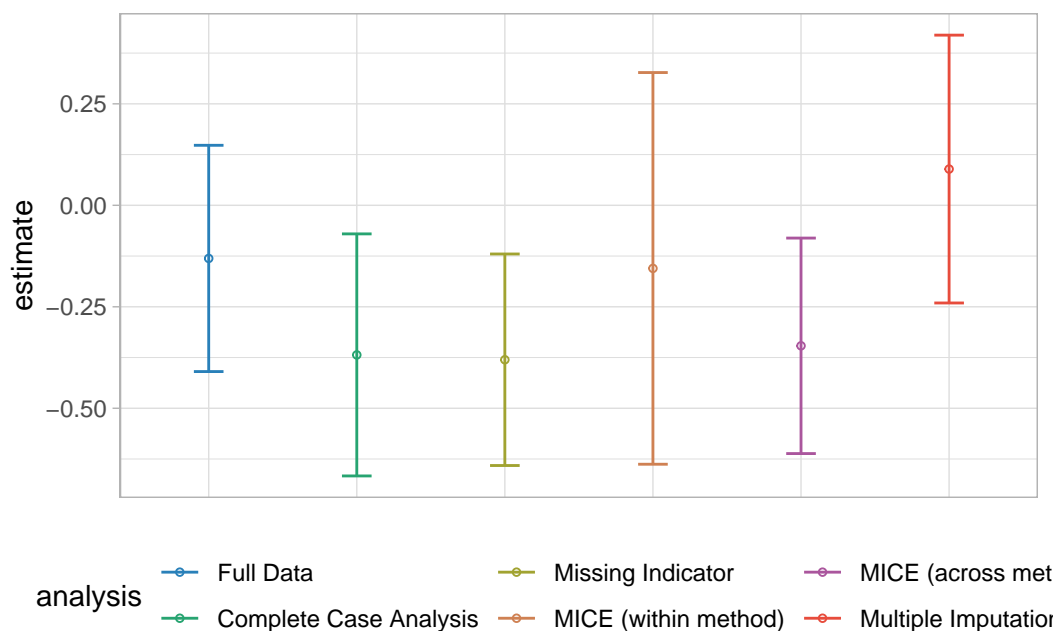


## 5.3 Results

Analysis methods:

- **Full Data:** The treatment effect is estimated in the original data of  $N = 3000$  patients where no missing values are present. This estimate can be used as a benchmark to compare the missing data methods.

- **Complete Case Analysis:** The treatment effect is estimated using all data from  $N = 946$  patients that do not have any missing values.
- **Missing Indicator:** The treatment effect is estimated in the incomplete dataset of  $N = 3000$  patients. The propensity score model includes a missing indicator variable for each incomplete covariate.
- **MICE (within method):** A treatment effect is estimated within each imputed dataset using propensity score analysis. Using Rubin's rule, the five treatment effects are combined into a single treatment effect.
- **MICE (ITE method):** The missing covariates and potential outcomes are imputed simultaneously. Treatment effect estimates are derived by taking the average of the individualized treatment effect estimates  $Y|DMF - Y|TERI$ .



## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19044)
```

```
Matrix products: default
```

locale:

```
[1] LC_COLLATE=Dutch_Netherlands.utf8 LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

attached base packages:

```
[1] grid      stats      graphics  grDevices utils      datasets  methods
[8] base
```

other attached packages:

```
[1] ggmmice_0.0.1      table1_1.4.3      kableExtra_1.3.4  ggplot2_3.4.2
[5] missForest_1.5     sandwich_3.0-2    PSweight_1.1.8    MatchThem_1.0.1
[9] mice_3.15.0        cobalt_4.5.1      WeightIt_0.14.1   MatchIt_4.5.3
[13] optmatch_0.10.6    truncnorm_1.0-9   MASS_7.3-58.3     survey_4.2-1
[17] survival_3.5-5     Matrix_1.5-4      data.table_1.14.8 tidyr_1.3.0
[21] dplyr_1.1.1
```

loaded via a namespace (and not attached):

```
[1] nlme_3.1-162      webshot_0.5.4      RColorBrewer_1.1-3
[4] httr_1.4.6        numDeriv_2016.8-1.1 tools_4.2.3
[7] backports_1.4.1   doRNG_1.8.6        utf8_1.2.3
[10] R6_2.5.1          DBI_1.1.3          colorspace_2.1-0
[13] nnet_7.3-19       withr_2.5.0        gbm_2.1.8.1
[16] tidyselect_1.2.0  compiler_4.2.3     cli_3.6.1
[19] rvest_1.0.3       see_0.7.5          xml2_1.3.3
[22] labeling_0.4.2    scales_1.2.1       nnls_1.4
[25] randomForest_4.7-1.1 systemfonts_1.0.4  stringr_1.5.0
[28] digest_0.6.31     minqa_1.2.5        rmarkdown_2.21
[31] svglite_2.1.1     pkgconfig_2.0.3    htmltools_0.5.5
[34] lme4_1.1-32       fastmap_1.1.1      itertools_0.1-3
[37] rlang_1.1.0       rstudioapi_0.14    generics_0.1.3
[40] farver_2.1.1      zoo_1.8-12         jsonlite_1.8.4
[43] magrittr_2.0.3    Formula_1.2-5      Rcpp_1.0.10
[46] munsell_0.5.0     fansi_1.0.4        lifecycle_1.0.3
[49] stringi_1.7.12    chk_0.8.1          yaml_2.3.7
[52] parallel_4.2.3    crayon_1.5.2       lattice_0.21-8
[55] splines_4.2.3     knitr_1.42         pillar_1.9.0
[58] boot_1.3-28.1     rngtools_1.5.2     codetools_0.2-19
[61] glue_1.6.2        evaluate_0.21      mitools_2.4
[64] vctrs_0.6.1       nloptr_2.0.3       foreach_1.5.2
[67] gtable_0.3.3      purrr_1.0.1        xfun_0.39
[70] SuperLearner_2.0-28 broom_1.0.4        viridisLite_0.4.2
```

|      |              |                  |            |
|------|--------------|------------------|------------|
| [73] | tibble_3.2.1 | iterators_1.0.14 | gam_1.22-2 |
| [76] | rlemon_0.2.1 |                  |            |

## 6 Systematic review and meta-analysis of Real-World Evidence

Dimitris Mavridis (University of Ioannina)

Thomas Debray (Smart Data Analysis and Statistics B.V.)

We first load the required packages

```
library(dplyr)
library(gemtc)
library(netmeta)
```

### 6.1 Pairwise meta-analysis of clinical trials

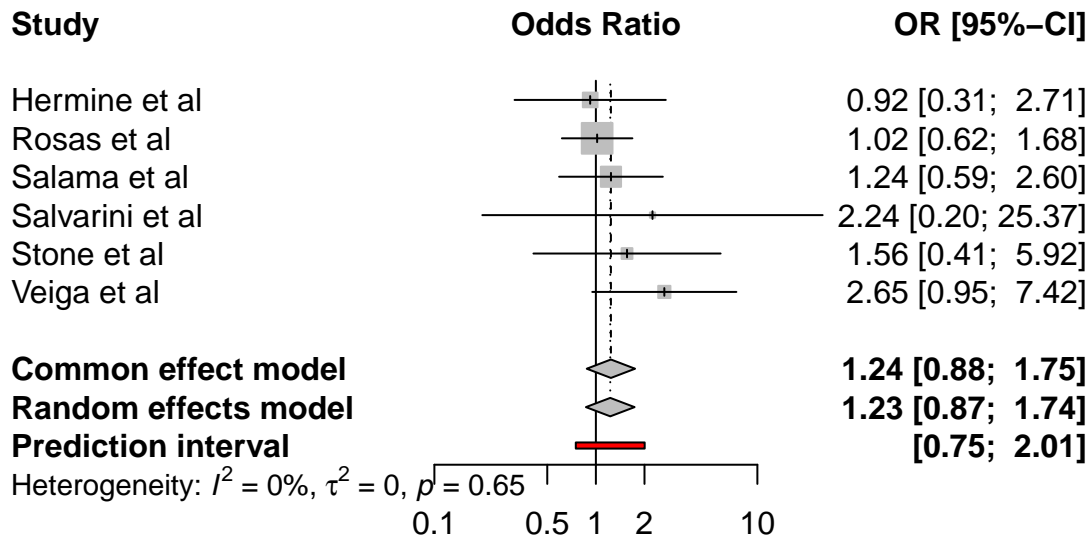
#### 6.1.1 Tocilizumab for coronavirus disease 2019

In this example, we consider the results from a systematic literature review of clinical trials investigating any pharmacological in hospitalized patients with coronavirus disease 2019 (Selvarajan et al. 2022). A total of 23 randomized controlled trials were included and studied seven different interventions: dexamethasone, remdesivir, tocilizumab, hydroxychloroquine, combination of lopinavir/ritonavir, favipiravir and interferon-. We here focus on the synthesis of 7 trials that compared tocilizumab (TOCI) to standard care (STD) and collected mortality data.

| studlab         | treat1 | treat2 | event1 | n1  | event2 | n2  |
|-----------------|--------|--------|--------|-----|--------|-----|
| Hermine et al   | TOCI   | STD    | 7      | 63  | 8      | 67  |
| Rosas et al     | TOCI   | STD    | 58     | 294 | 28     | 144 |
| Salama et al    | TOCI   | STD    | 26     | 249 | 11     | 128 |
| Salvarini et al | TOCI   | STD    | 2      | 60  | 1      | 66  |
| Stone et al     | TOCI   | STD    | 9      | 161 | 3      | 82  |
| Veiga et al     | TOCI   | STD    | 14     | 65  | 6      | 64  |

We now conduct a pairwise meta-analysis to assess the pooled effect of tocilizumab versus standard care. For each study, the log odds ratio and corresponding standard error is derived after which the corresponding estimates are pooled using the Mantel-Haenszel method.

```
results.TOCI <- metabin(event1,n1,event2,n2,studlab,data=tocilizumab,
                        sm="OR",main="tocilizumab vs standard care",
                        prediction=TRUE)
forest(results.TOCI, leftcols = "studlab", rightcols = "effect.ci")
```

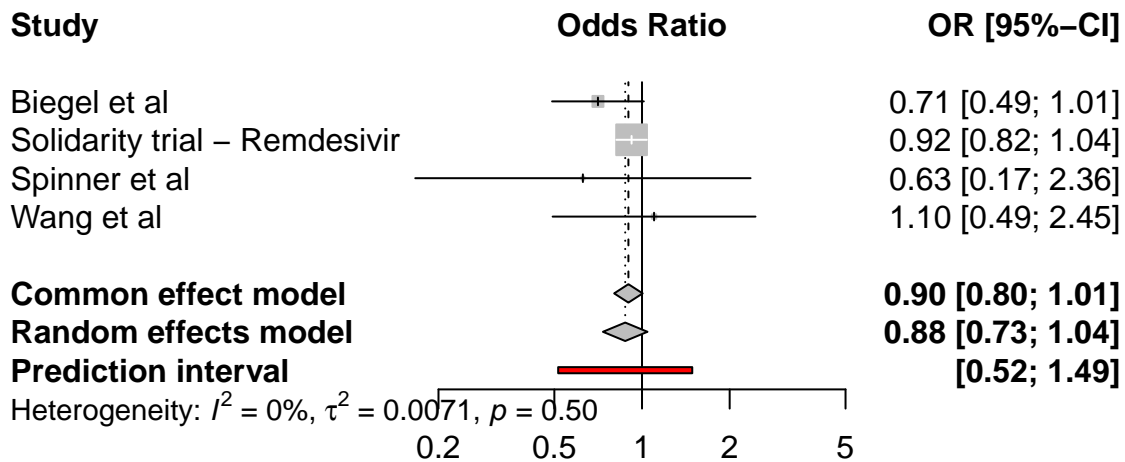


Although a random effects meta-analysis was conducted, no heterogeneity was found ( $\tau=0$ , with a 95% confidence interval ranging from 0 to 0.85).



### 6.1.2 Remdesivir for coronavirus disease 2019

In aforementioned example, a total of 4 trials compared remdesivir to standard care:



## 6.2 Network meta-analysis of clinical trials

We here use the R packages `netmeta` for conducting a frequentist network meta-analysis. A detailed tutorial on the use of `netmeta` is available from the book [Doing Meta-Analysis with R: A Hands-On Guide](#).

### 6.2.1 Interventions for coronavirus disease 2019

We here consider data from a study which aimed to assess the comparative effectiveness of remdesivir and tocilizumab for reducing mortality in hospitalised COVID-19 patients. 80 trials were identified from two published network meta-analyses (Selvarajan et al. 2022), (Siemieniuk et al. 2020), a living COVID-19 trial database (COVID-NMA Initiative) [Covid-NMA.com], and a clinical trial database [clinicaltrials.gov]. Trials were included in this study if the patient population included hospitalized COVID-19 patients, active treatment was remdesivir or tocilizumab, comparator treatment was placebo or standard care, short-term mortality data was available, and the trial was published. 21 trials were included. For included trials, a risk of bias score was extracted from the COVID-NMA Initiative.

| studlab              | treat1 | treat2 | event1 | n1   | event2 | n2   |
|----------------------|--------|--------|--------|------|--------|------|
| Ader                 | REM    | STD    | 34     | 414  | 37     | 418  |
| Beigel (ACTT-1)      | REM    | STD    | 59     | 541  | 77     | 521  |
| Broman               | TOCI   | STD    | 1      | 57   | 0      | 29   |
| Criner               | REM    | STD    | 4      | 384  | 4      | 200  |
| Declerq (COV-AID)    | TOCI   | STD    | 10     | 81   | 9      | 74   |
| Gordon (REMAP-CAP)   | TOCI   | STD    | 83     | 353  | 116    | 358  |
| Hermine (CORIMUNO)   | TOCI   | STD    | 7      | 63   | 8      | 67   |
| Horby (RECOVERY)     | TOCI   | STD    | 621    | 2022 | 729    | 2094 |
| Islam                | REM    | STD    | 0      | 30   | 0      | 30   |
| Mahajan              | REM    | STD    | 5      | 34   | 3      | 36   |
| Pan (WHO Solidarity) | REM    | STD    | 602    | 4146 | 643    | 4129 |
| Rosas (COVACTA)      | TOCI   | STD    | 58     | 294  | 28     | 144  |
| Rutgers              | TOCI   | STD    | 21     | 174  | 34     | 180  |
| Salama (EMPACTA)     | TOCI   | STD    | 26     | 249  | 11     | 128  |
| Salvarani            | TOCI   | STD    | 2      | 60   | 1      | 63   |
| Soin (COVINTOC)      | TOCI   | STD    | 11     | 92   | 15     | 88   |
| Spinner              | REM    | STD    | 5      | 384  | 4      | 200  |
| Stone (BACC-BAY)     | TOCI   | STD    | 9      | 161  | 4      | 82   |
| Talaschian           | TOCI   | STD    | 5      | 17   | 4      | 19   |
| Veiga (TOCIBRAS)     | TOCI   | STD    | 14     | 65   | 6      | 64   |
| Wang                 | REM    | STD    | 22     | 158  | 10     | 78   |

The corresponding network is displayed below:

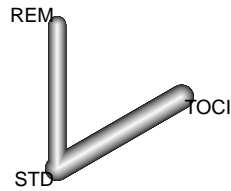


Figure 6.1: Evidence network of the 21 coronavirus-19 trials

We use the following command to calculate the log odds ratios and corresponding standard errors for each study:

```
covid <- pairwise(treat = treat, event = event, n = n, studlab = studlab, sm = "OR")
head(covid)
```

| TE         | seTE      | studlab            | treat1 | treat2 | event1 | n1  | event2 | n2  | incr | alls |
|------------|-----------|--------------------|--------|--------|--------|-----|--------|-----|------|------|
| -0.0819293 | 0.2483849 | Ader               | REM    | STD    | 34     | 414 | 37     | 418 | 0.0  | FAI  |
| -0.3483875 | 0.1851030 | Beigel (ACTT-1)    | REM    | STD    | 59     | 541 | 77     | 521 | 0.0  | FAI  |
| 0.4487619  | 1.6487159 | Broman             | TOCI   | STD    | 1      | 57  | 0      | 29  | 0.5  | FAI  |
| -0.6620566 | 0.7125543 | Criner             | REM    | STD    | 4      | 384 | 4      | 200 | 0.0  | FAI  |
| 0.0170679  | 0.4904898 | Declerq (COV-AID)  | TOCI   | STD    | 10     | 81  | 9      | 74  | 0.0  | FAI  |
| -0.4442338 | 0.1688337 | Gordon (REMAP-CAP) | TOCI   | STD    | 83     | 353 | 116    | 358 | 0.0  | FAI  |

Below, we conduct a random effects network meta-analysis where we consider standard care (STD) as the control treatment. Note that we have one study where zero cell counts occur, this study will not contribute to the NMA as the log odds ratio and its standard error cannot be determined.

```
NMA.covid <- netmeta(TE = TE, seTE = seTE, treat1 = treat1, treat2 = treat2,
  studlab = studlab, data = covid, sm = "OR", ref = "STD",
  comb.random = TRUE, common = FALSE, warn = FALSE)

NMA.covid
```

Number of studies: k = 20  
 Number of pairwise comparisons: m = 20  
 Number of treatments: n = 3  
 Number of designs: d = 2

Random effects model

Treatment estimate (sm = 'OR', comparison: other treatments vs 'STD'):

|      | OR     | 95%-CI           | z     | p-value |
|------|--------|------------------|-------|---------|
| REM  | 0.8999 | [0.8067; 1.0039] | -1.89 | 0.0588  |
| STD  | .      | .                | .     | .       |
| TOCI | 0.8301 | [0.7434; 0.9268] | -3.31 | 0.0009  |

Quantifying heterogeneity / inconsistency:

$\tau^2 = 0$ ;  $\tau = 0$ ;  $I^2 = 0\%$  [0.0%; 48.9%]

Tests of heterogeneity (within designs) and inconsistency (between designs):

|                 | Q     | d.f. | p-value |
|-----------------|-------|------|---------|
| Total           | 16.38 | 18   | 0.5663  |
| Within designs  | 16.38 | 18   | 0.5663  |
| Between designs | 0.00  | 0    | --      |

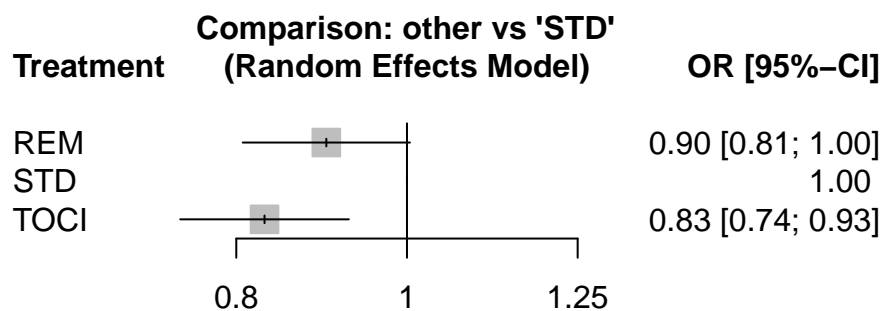
A league table of the treatment effect estimates is given below:

```
netleague(NMA.covid)
```

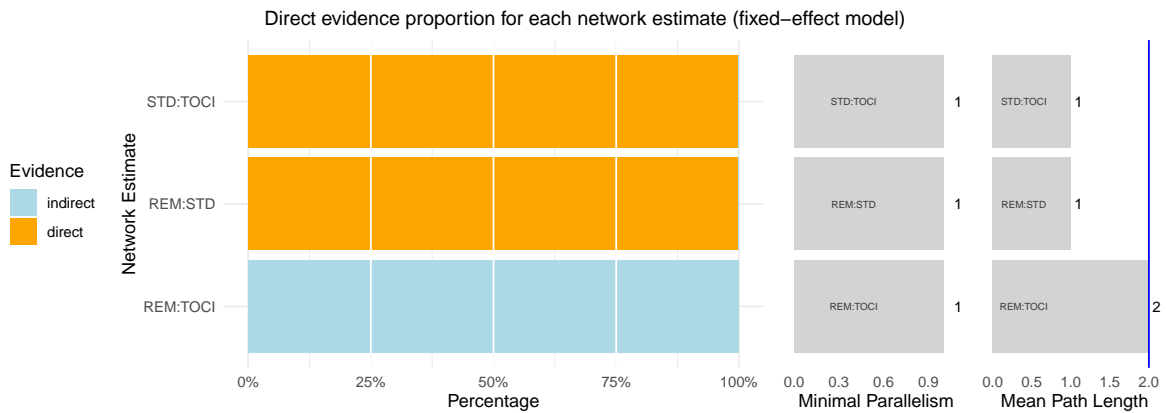
League table (random effects model):

|                         |                             |                             |      |
|-------------------------|-----------------------------|-----------------------------|------|
|                         | REM 0.8999 [0.8067; 1.0039] |                             | .    |
| 0.8999 [0.8067; 1.0039] |                             | STD 1.2047 [1.0789; 1.3451] |      |
| 1.0842 [0.9282; 1.2663] | 1.2047 [1.0789; 1.3451]     |                             | TOCI |

We can also present the results in a forest plot:



The figure below shows the percentage of direct and indirect evidence used for each estimated comparison.



We now consider a Bayesian random effects network meta-analysis that analyzes the observed event counts using a binomial link function.

```
bdata <- data.frame(study = studlab,
                     treatment = treat,
                     responders = event,
                     sampleSize = n)

network <- mtc.network(data.ab = bdata)

model <- mtc.model(network,
                    likelihood = "binom",
                    link = "log",
                    linearModel = "random",
                    n.chain = 3)

# Adaptation
mcmc1 <- mtc.run(model, n.adapt = 1000, n.iter = 1000, thin = 10)
```

Compiling model graph

Resolving undeclared variables

Allocating nodes

Graph information:

Observed stochastic nodes: 42

Unobserved stochastic nodes: 45

Total graph size: 930

Initializing model

```
# Sampling
mcmc2 <- mtc.run(model, n.adapt = 10000, n.iter = 100000, thin = 10)
```

```
Compiling model graph
  Resolving undeclared variables
  Allocating nodes
Graph information:
  Observed stochastic nodes: 42
  Unobserved stochastic nodes: 45
  Total graph size: 930
```

```
Initializing model
```

We can extract the pooled treatment effect estimates from the posterior distribution. When using STD as control group, we have:

```
summary(relative.effect(mcmc2, t1 = "STD"))
```

Results on the Log Risk Ratio scale

```
Iterations = 10010:110000
Thinning interval = 10
Number of chains = 3
Sample size per chain = 10000
```

1. Empirical mean and standard deviation for each variable,  
plus standard error of the mean:

|            | Mean    | SD      | Naive SE  | Time-series SE |
|------------|---------|---------|-----------|----------------|
| d.STD.REM  | -0.1083 | 0.09805 | 0.0005661 | 0.0008072      |
| d.STD.TOCI | -0.1109 | 0.08315 | 0.0004800 | 0.0008498      |
| sd.d       | 0.1134  | 0.08883 | 0.0005129 | 0.0018761      |

2. Quantiles for each variable:

|            | 2.5%     | 25%      | 50%      | 75%      | 97.5%   |
|------------|----------|----------|----------|----------|---------|
| d.STD.REM  | -0.31694 | -0.16154 | -0.10534 | -0.05205 | 0.08566 |
| d.STD.TOCI | -0.25663 | -0.16159 | -0.11886 | -0.06907 | 0.08273 |
| sd.d       | 0.00275  | 0.04497  | 0.09498  | 0.16190  | 0.33112 |

The corresponding odds ratios are as follows:

| Comparison   | 95% CrI           |
|--------------|-------------------|
| REM vs. STD  | 0.9 (0.73; 1.09)  |
| TOCI vs. STD | 0.89 (0.77; 1.09) |
| REM vs. TOCI | 1.01 (0.74; 1.27) |

Finally, we expand the COVID-19 network with trials investigating the effectiveness of hydroxychloroquine (HCQ), lopinavir/ritonavir (LOPI), dexamethasone (DEXA) or interferon- $\beta$  (INTB) (Selvarajan et al. 2022). The corresponding network is displayed below:

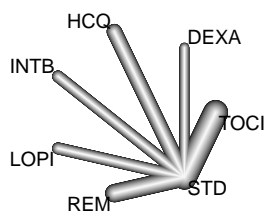


Figure 6.2: Evidence network of the 33 coronavirus-19 trials

We conducted a random effects network meta-analysis, results are depicted below:

Number of studies:  $k = 33$

Number of pairwise comparisons:  $m = 33$

Number of treatments:  $n = 7$

Number of designs:  $d = 6$

Random effects model

Treatment estimate (sm = 'OR', comparison: other treatments vs 'STD'):

|      | OR     | 95%-CI           | z     | p-value | 95%-PI           |
|------|--------|------------------|-------|---------|------------------|
| DEXA | 0.8557 | [0.7558; 0.9688] | -2.46 | 0.0139  | [0.7463; 0.9812] |
| HCQ  | 1.1809 | [0.8934; 1.5610] | 1.17  | 0.2428  | [0.8786; 1.5872] |
| INTB | 1.1606 | [0.9732; 1.3841] | 1.66  | 0.0973  | [0.9604; 1.4026] |
| LOPI | 1.0072 | [0.8906; 1.1392] | 0.11  | 0.9085  | [0.8794; 1.1537] |
| REM  | 0.8983 | [0.8014; 1.0070] | -1.84 | 0.0658  | [0.7913; 1.0199] |

```
STD
TOCI 0.8304 [0.7410; 0.9306] -3.20 0.0014 [0.7316; 0.9426]
```

Quantifying heterogeneity / inconsistency:  
 $\tau^2 = 0.0004$ ;  $\tau = 0.0205$ ;  $I^2 = 0.6\%$  [0.0%; 42.3%]

Tests of heterogeneity (within designs) and inconsistency (between designs):

|                 | Q     | d.f. | p-value |
|-----------------|-------|------|---------|
| Total           | 27.18 | 27   | 0.4543  |
| Within designs  | 27.18 | 27   | 0.4543  |
| Between designs | 0.00  | 0    | --      |

We can calculate the P score for each treatment as follows:

```
netrank(NMA.covidf)
```

|      | P-score |
|------|---------|
| TOCI | 0.9070  |
| DEXA | 0.8357  |
| REM  | 0.7143  |
| STD  | 0.4027  |
| LOPI | 0.3899  |
| HCQ  | 0.1336  |
| INTB | 0.1166  |

## 6.2.2 Pharmacologic treatments for chronic obstructive pulmonary disease

In this example, we consider the results from a systematic review of randomized controlled trials on pharmacologic treatments for chronic obstructive pulmonary disease (Baker, Baker, and Coleman 2009). The primary outcome, occurrence of one or more episodes of COPD exacerbation, is binary (yes / no). For this outcome, five drug treatments (fluticasone, budesonide, salmeterol, formoterol, tiotropium) and two combinations (fluticasone + salmeterol, budesonide + formoterol) were compared to placebo. The authors considered the two combinations as separate treatments instead of evaluating the individual components.

```
data(Baker2009)
```



| study                | year | id | treatment   | exac | total |
|----------------------|------|----|-------------|------|-------|
| Llewellyn-Jones 1996 | 1996 | 1  | Fluticasone | 0    | 8     |
| Llewellyn-Jones 1996 | 1996 | 1  | Placebo     | 3    | 8     |
| Boyd 1997            | 1997 | 2  | Salmeterol  | 47   | 229   |
| Boyd 1997            | 1997 | 2  | Placebo     | 59   | 227   |
| Paggiaro 1998        | 1998 | 3  | Fluticasone | 45   | 142   |
| Paggiaro 1998        | 1998 | 3  | Placebo     | 51   | 139   |

```
Baker <- pairwise(treat = treatment,
                  event = exac,
                  n = total,
                  studlab = id,
                  sm = "OR",
                  data = Baker2009)

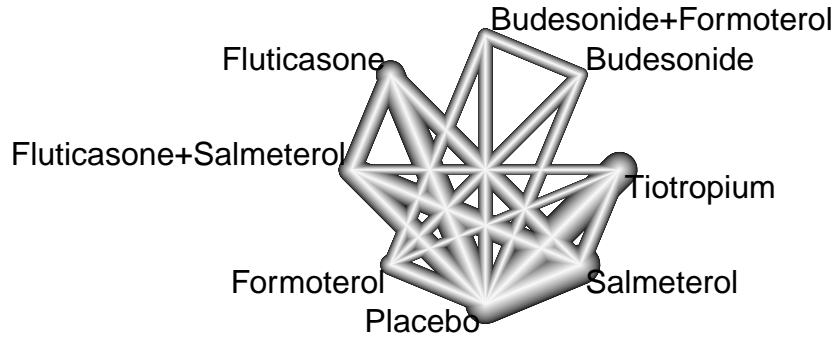
NMA.COPD <- netmeta(TE = TE, seTE = seTE, treat1 = treat1, treat2 = treat2,
                  studlab = studlab, data = Baker, sm="OR", ref = "Placebo",
                  comb.random = TRUE)
```

Warning: Comparisons with missing TE / seTE or zero seTE not considered in network meta-analysis.

Comparisons not considered in network meta-analysis:

| studlab                   | treat1     | treat2  | TE | seTE |
|---------------------------|------------|---------|----|------|
| 39 Fluticasone+Salmeterol | Placebo    | NA      | NA | NA   |
| 39 Fluticasone+Salmeterol | Salmeterol | NA      | NA | NA   |
| 39                        | Salmeterol | Placebo | NA | NA   |

```
netgraph(NMA.COPD)
```



### 6.2.3 Advanced Therapies for Ulcerative Colitis

In this example, we consider a systematic literature review of Phase 3 randomized controlled trials investigating the following advanced therapies: infliximab, adalimumab, vedolizumab, golimumab, tofacitinib, ustekinumab, filgotinib, ozanimod, and upadacitinib (Panaccione et al. 2023). This review included 48 RCTs, from which 23 were found eligible for inclusion in a network meta-analysis. The included RCT populations were largely comparable in their baseline characteristics, though some heterogeneity was noted in weight, disease duration, extent of disease, and concomitant medications. A risk of bias assessment showed a low risk of bias for all included RCTs, which were all industry sponsored.

We here focus on the synthesis of 18 trials that contributed efficacy data for induction in bio-naive populations. The following FDA- and/or EMA-approved biologic or SMD doses were investigated:

- Adalimumab subcutaneous 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 (ADA160/80)
- Infliximab intravenous 5 mg/kg (INF5) at weeks 0, 2, and 6 then every 8 weeks
- Infliximab intravenous 10 mg/kg (INF10) at weeks 0, 2, and 6 then every 8 weeks
- Filgotinib oral 100 mg once daily (FIL100)
- Filgotinib oral 200 mg once daily (FIL200)
- Golimumab subcutaneous 200 mg at week 0 and 100 mg at week 2 (GOL200/100)

- Ozanimod oral 0.23 mg once daily for 4 days, 0.46 mg once daily for 3 days, then 0.92 mg once daily (OZA0.92)
- Tofacitinib oral 10 mg twice daily for 8 weeks (TOF10)
- Upadacitinib oral 45 mg once daily for 8 weeks (UPA45)
- Ustekinumab intravenous 6 mg/kg at week 0 (UST6)
- Vedolizumab intravenous 300 mg at weeks 0, 2, and 6 (VED300)

The reference treatment is placebo (PBO).

Table 6.4: Efficacy outcomes (i.e., clinical remission) data of induction bio-naïve populations

| studlab           | treat1     | treat2 | event1 | n1  | event2 | n2  |
|-------------------|------------|--------|--------|-----|--------|-----|
| ACT-1             | INF10      | INF5   | 39     | 122 | 47     | 121 |
| ACT-1             | INF10      | PBO    | 39     | 122 | 18     | 121 |
| ACT-1             | INF5       | PBO    | 47     | 121 | 18     | 121 |
| ACT-2             | INF10      | INF5   | 33     | 120 | 41     | 121 |
| ACT-2             | INF10      | PBO    | 33     | 120 | 7      | 123 |
| ACT-2             | INF5       | PBO    | 41     | 121 | 7      | 123 |
| GEMINI 1          | VED300     | PBO    | 30     | 130 | 5      | 76  |
| Japic CTI-060298  | INF5       | PBO    | 21     | 104 | 11     | 104 |
| Jiang 2015        | INF5       | PBO    | 22     | 41  | 9      | 41  |
| M10-447           | ADA160/80  | PBO    | 9      | 90  | 11     | 96  |
| NCT01551290       | INF5       | PBO    | 11     | 50  | 5      | 49  |
| NCT02039505       | VED300     | PBO    | 22     | 79  | 6      | 41  |
| OCTAVE 1          | TOF10      | PBO    | 56     | 222 | 9      | 57  |
| OCTAVE 2          | TOF10      | PBO    | 43     | 195 | 4      | 47  |
| PURSUIT-SC        | GOL200/100 | PBO    | 45     | 253 | 16     | 251 |
| SELECTION         | FIL100     | FIL200 | 47     | 277 | 60     | 245 |
| SELECTION         | FIL100     | PBO    | 47     | 277 | 17     | 137 |
| SELECTION         | FIL200     | PBO    | 60     | 245 | 17     | 137 |
| TRUE NORTH        | OZA0.92    | PBO    | 66     | 299 | 10     | 151 |
| U-ACCOMPLISH      | UPA45      | PBO    | 54     | 166 | 3      | 81  |
| U-ACHIEVE Study 2 | UPA45      | PBO    | 41     | 145 | 4      | 72  |
| ULTRA-1           | ADA160/80  | PBO    | 24     | 130 | 12     | 130 |
| ULTRA-2           | ADA160/80  | PBO    | 32     | 150 | 16     | 145 |
| UNIFI             | UST6       | PBO    | 27     | 147 | 15     | 151 |

The corresponding network is displayed below:

Below, we conduct a random effects network meta-analysis of the reported study effects (expressed as odds ratio) and consider placebo (`treat = "PBO"`) as the control treatment.

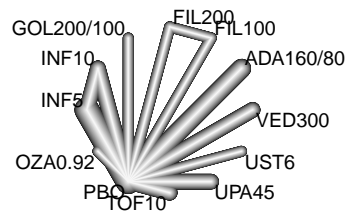


Figure 6.3: Evidence network of 18 trials that contributed efficacy data for induction in bio-naive populations

```
NMA.uc <- netmeta(TE = TE, seTE = seTE, treat1 = treat1, treat2 = treat2,
  studlab = studlab, data = UlcerativeColitis, sm = "OR",
  ref = "PBO", common = FALSE, comb.random = TRUE)

NMA.uc
```

All treatments except FIL100 and UST6 are significantly more efficacious than PBO at inducing clinical remission. We can now estimate the probabilities of each treatment being at each possible rank and the SUCRAs (Surface Under the Cumulative RAnking curve):

```
sucra.uc <- rankogram(NMA.uc, nsim = 100, random = TRUE, common = FALSE,
  small.values = "undesirable")

# Extract the SUCRA values
sucra.uc$ranking.random
```

|            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|
| ADA160/80  | FIL100     | FIL200     | GOL200/100 | INF10      | INF5       | OZA0.92    |
| 0.25909091 | 0.15272727 | 0.44090909 | 0.67363636 | 0.56636364 | 0.74727273 | 0.77090909 |
| PBO        | TOF10      | UPA45      | UST6       | VED300     |            |            |
| 0.01636364 | 0.37909091 | 0.97909091 | 0.38909091 | 0.62545455 |            |            |

These results indicate that 97.9% of the evaluated treatments are worse than UPA45.

## Version info

This chapter was rendered using the following version of R and its packages:

R version 4.2.3 (2023-03-15 ucrt)  
Platform: x86\_64-w64-mingw32/x64 (64-bit)  
Running under: Windows 10 x64 (build 19044)

Matrix products: default

locale:

[1] LC\_COLLATE=Dutch\_Netherlands.utf8 LC\_CTYPE=Dutch\_Netherlands.utf8  
[3] LC\_MONETARY=Dutch\_Netherlands.utf8 LC\_NUMERIC=C  
[5] LC\_TIME=Dutch\_Netherlands.utf8

attached base packages:

[1] stats graphics grDevices utils datasets methods base

other attached packages:

[1] dmetar\_0.0.9000 netmeta\_2.8-2 meta\_6.2-1 gemtc\_1.0-1  
[5] coda\_0.19-4 dplyr\_1.1.1 kableExtra\_1.3.4

loaded via a namespace (and not attached):

|                        |                 |                     |
|------------------------|-----------------|---------------------|
| [1] httr_1.4.6         | magic_1.6-1     | jsonlite_1.8.4      |
| [4] viridisLite_0.4.2  | splines_4.2.3   | stats4_4.2.3        |
| [7] metafor_4.0-0      | slam_0.1-50     | yaml_2.3.7          |
| [10] robustbase_0.95-1 | ggrepel_0.9.3   | numDeriv_2016.8-1.1 |
| [13] pillar_1.9.0      | lattice_0.21-8  | glue_1.6.2          |
| [16] digest_0.6.31     | rvest_1.0.3     | minqa_1.2.5         |
| [19] colorspace_2.1-0  | MuMIn_1.47.5    | htmltools_0.5.5     |
| [22] Matrix_1.5-4      | plyr_1.8.8      | pkgconfig_2.0.3     |
| [25] mvtnorm_1.1-3     | Rglpk_0.6-5     | scales_1.2.1        |
| [28] webshot_0.5.4     | svglite_2.1.1   | rjags_4-14          |
| [31] metadat_1.2-0     | lme4_1.1-32     | tibble_3.2.1        |
| [34] farver_2.1.1      | generics_0.1.3  | ggplot2_3.4.2       |
| [37] withr_2.5.0       | nnet_7.3-19     | cli_3.6.1           |
| [40] magrittr_2.0.3    | mclust_6.0.0    | evaluate_0.21       |
| [43] fansi_1.0.4       | nlme_3.1-162    | MASS_7.3-58.3       |
| [46] truncnorm_1.0-9   | forcats_1.0.0   | xml2_1.3.3          |
| [49] class_7.3-22      | tools_4.2.3     | lifecycle_1.0.3     |
| [52] stringr_1.5.0     | kernlab_0.9-32  | munSELL_0.5.0       |
| [55] cluster_2.1.4     | fpc_2.2-10      | compiler_4.2.3      |
| [58] systemfonts_1.0.4 | rlang_1.1.0     | grid_4.2.3          |
| [61] nloptr_2.0.3      | rstudioapi_0.14 | CompQuadForm_1.4.3  |
| [64] igraph_1.4.2      | labeling_0.4.2  | rmarkdown_2.21      |
| [67] boot_1.3-28.1     | gtable_0.3.3    | codetools_0.2-19    |
| [70] abind_1.4-5       | flexmix_2.3-19  | R6_2.5.1            |

|      |                 |                   |                |
|------|-----------------|-------------------|----------------|
| [73] | gridExtra_2.3   | knitr_1.42        | prabclus_2.3-2 |
| [76] | fastmap_1.1.1   | utf8_1.2.3        | mathjaxr_1.6-0 |
| [79] | poibin_1.5      | modeltools_0.2-23 | stringi_1.7.12 |
| [82] | parallel_4.2.3  | Rcpp_1.0.10       | vctrs_0.6.1    |
| [85] | DEoptimR_1.0-13 | tidyselect_1.2.0  | xfun_0.39      |
| [88] | diptest_0.76-0  |                   |                |

## References

## 7 Dealing with irregular and informative visits

We first load the required packages

```
library(dplyr)
library(broom)
library(ggplot2)
library(mice)
```

### 7.1 Example dataset

Below, we generate an example dataset that contains information on the treatment allocation `x` and three baseline covariates `age`, `sex` and `edss` (EDSS at treatment start). The discrete outcome `y` represents the Expanded Disability Status Scale (EDSS) score after `time` months of treatment exposure. Briefly, the EDSS is a semi-continuous measure that varies from 0 (no disability) to 10 (death).

```
set.seed(9843626)

dataset <- sim_data_EDSS(npatients = 500,
  ncenters = 10,
  follow_up = 12*5, # Total follow-up (number of months)
  sd_a_t = 0.5,     # DGM - Within-visit variation in EDSS scores
  baseline_EDSS = 1.3295, # DGM - Mean baseline EDDS score
  sd_alpha_ij = 1.46, # DGM - Between-subject variation in base
  sd_beta1_j = 0.20,  # DGM - Between-site variation in baseline
  mean_age = 42.41,
  sd_age = 10.53,
  min_age = 18,
  beta_age = 0.05, # DGM - prognostic effect of age
  beta_t = 0.014, # DGM - prognostic effect of time
  beta_t2 = 0,    # DGM - prognostic effect of time squared
  delta_xt = 0,  # DGM - interaction treatment time
  delta_xt2 = 0, # 0.0005 # DGM - interaction treatment time2
```

```

p_female = 0.75,
beta_female = -0.2 , ## DGM - prognostic effect of male sex
delta_xf = 0,      ## DGM - interaction sex treatment
rho = 0.8,          # DGM - autocorrelation of between alpha_
corFUN = corAR1,    # DGM - correlation structure of the late
tx_alloc_FUN = treatment_alloc_confounding_v2 ) ## or treatment_

```

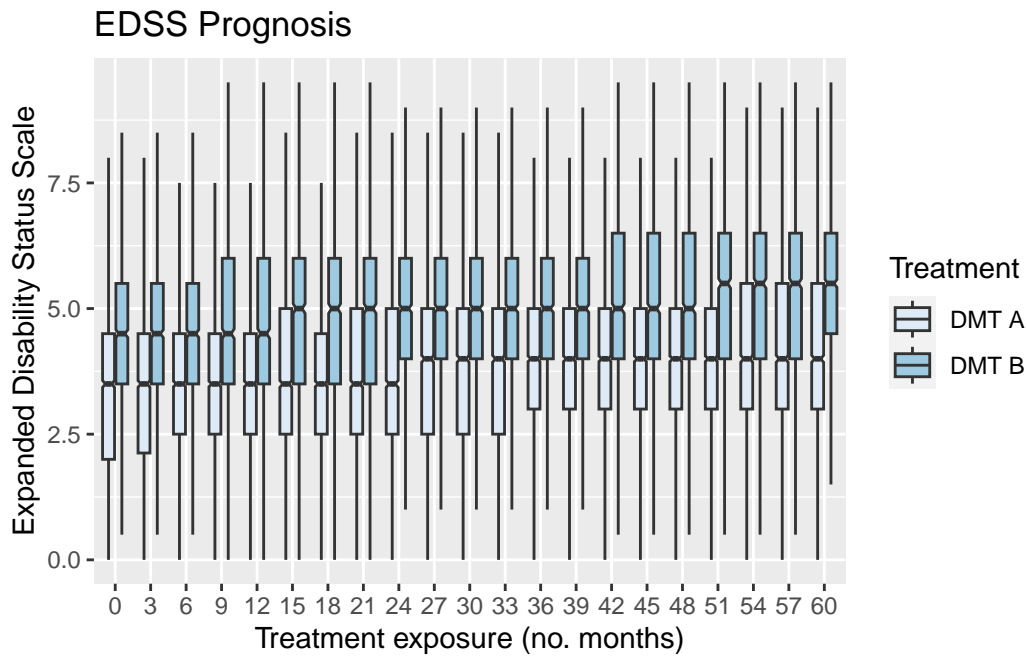


Figure 7.1: Distribution of the EDSS score at each time point

We remove the outcome  $y$  according to the informative visit process that depends on the received treatment, gender, and age.

```

dataset_visit <- censor_visits_a5(dataset, seed = 12345) %>%
  dplyr::select(-y) %>%
  mutate(time_x = time*x)

```

In the censored data, a total of 17 out of 5000 patients have a visit at `time=60`.

## 7.2 Estimation of treatment effect

We will estimate the marginal treatment effect at time `time=60`.



### 7.2.1 Original data

```
origdat60 <- dataset %>% filter(time == 60)

# Predict probability of treatment allocation
fitps <- glm(x ~ age + sex + edss, family = 'binomial',
             data = origdat60)

# Derive the propensity score
origdat60 <- origdat60 %>% mutate(ipt = ifelse(x == 1, 1/predict(fitps, type = 'response'),
                                              1/(1-predict(fitps, type = 'response'))))

# Estimate
fit_ref_m <- tidy(lm(y ~ x, weight = ipt, data = origdat60), conf.int = TRUE)
```

### 7.2.2 Doubly-weighted marginal treatment effect

```
obsdat60 <- dataset_visit %>% mutate(visit = ifelse(is.na(y_obs),0,1)) %>% filter(time ==

gamma <- glm(visit ~ x + sex + age + edss, family = 'binomial', data = obsdat60)$coef

obsdat60 <- obsdat60 %>% mutate(rho_i = 1/exp(gamma["(Intercept)"] +
                                             gamma["x"]*x +
                                             gamma["sex"]*sex +
                                             gamma["age"]*age))

# Predict probability of treatment allocation
fitps <- glm(x ~ age + sex + edss, family='binomial', data = obsdat60)

# Derive the propensity score
obsdat60 <- obsdat60 %>% mutate(ipt = ifelse(x==1, 1/predict(fitps, type='response'),
                                              1/(1-predict(fitps, type='response'))))

fit_w <- tidy(lm(y_obs ~ x, weights = ipt*rho_i, data = obsdat60), conf.int = TRUE)
```

### 7.2.3 Multilevel multiple imputation

We impute the entire vector of `y_obs` for all 61 potential visits and generate 10 imputed datasets. Note: `mlmi` currently does not support imputation of treatment-covariate interaction terms.

```
imp <- impute_y_mice_3l(dataset_visit, seed = 12345)
```

We can now estimate the treatment effect in each imputed dataset

```
# Predict probability of treatment allocation
fitps <- glm(x ~ age + sex + edss, family='binomial', data = dataset_visit)

# Derive the propensity score
dataset_visit <- dataset_visit %>% mutate(ipt = ifelse(x==1, 1/predict(fitps, type='response'),
                                                    1/(1-predict(fitps, type='response'))))

Q <- U <- rep(NA, 10) # Error variances

for (i in seq(10)) {
  dati <- cbind(dataset_visit[,c("x","ipt","time")], y_imp = imp[,i]) %>% filter(time == 6)

  # Estimate
  fit <- tidy(lm(y_imp ~ x, weight = ipt, data = dati), conf.int = TRUE)

  Q[i] <- fit %>% filter(term == "x") %>% pull(estimate)
  U[i] <- (fit %>% filter(term == "x") %>% pull(std.error))**2
}

fit_mlmi <- pool.scalar(Q = Q, U = U)
```

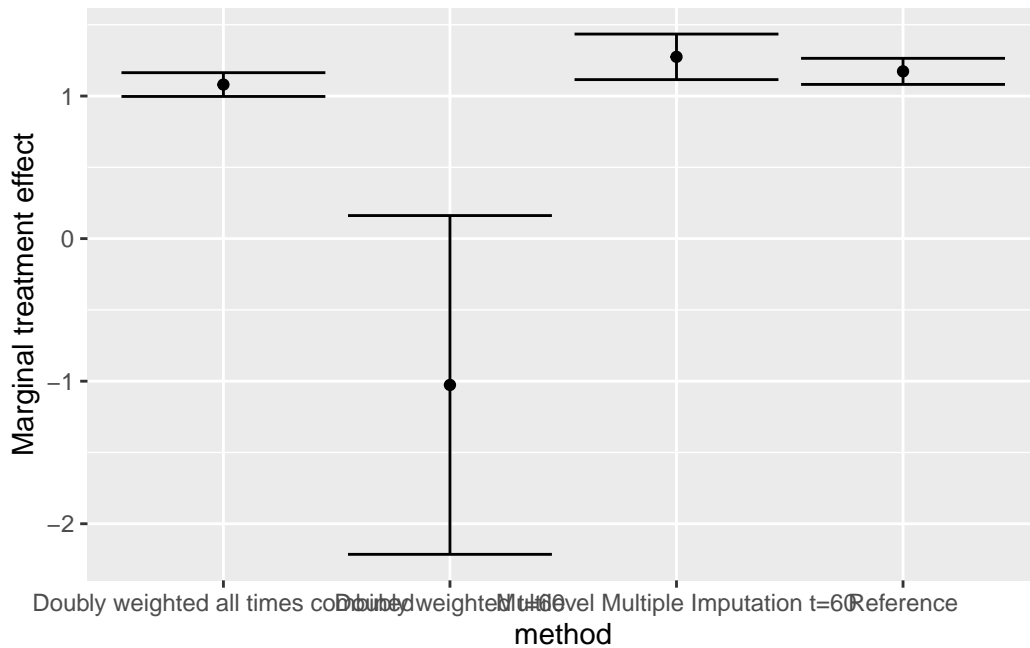
## 7.3 Reproduce the results using all data to compute the marginal effect with IIV-weighted

### 7.3.1 Doubly -weighted marginal treatment effect total

```
obsdatall <- dataset_visit %>% mutate(visit = ifelse(is.na(y_obs),0,1))
gamma <- glm(visit ~ x + sex + age + edss, family = 'binomial', data = obsdatall)$coef
obsdatall <- obsdatall %>% mutate(rho_i = 1/exp(gamma["(Intercept)"] +
      gamma["x"]*x +
      gamma["sex"]*sex +
      gamma["age"]*age))

# Predict probability of treatment allocation
fitps <- glm(x ~ age + sex + edss, family='binomial', data = obsdatall)
# Derive the propensity score
obsdatall <- obsdatall %>% mutate(ipt = ifelse(x==1, 1/predict(fitps, type='response'),
      1/(1-predict(fitps, type='response'))))
fit_w <- tidy(lm(y_obs ~ x, weights = ipt*rho_i, data = obsdatall), conf.int = TRUE)
```

## 7.4 Results



## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19045)
```

```
Matrix products: default
```

```
locale:
```

```
[1] LC_COLLATE=Dutch_Netherlands.utf8  LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

```
attached base packages:
```

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

```
other attached packages:
```

```
[1] broom_1.0.4      mice_3.15.0      ggplot2_3.4.2    dplyr_1.1.1
[5] truncnorm_1.0-9 MASS_7.3-58.3    nlme_3.1-162
```

```
loaded via a namespace (and not attached):
```

```
[1] Rcpp_1.0.10      RColorBrewer_1.1-3 pillar_1.9.0      compiler_4.2.3
[5] tools_4.2.3      digest_0.6.31     jsonlite_1.8.4    evaluate_0.21
[9] lifecycle_1.0.3  tibble_3.2.1      gtable_0.3.3      lattice_0.21-8
[13] pkgconfig_2.0.3  rlang_1.1.0       cli_3.6.1          rstudioapi_0.14
[17] yaml_2.3.7       xfun_0.39         fastmap_1.1.1     withr_2.5.0
[21] knitr_1.42       generics_0.1.3    vctrs_0.6.1       grid_4.2.3
[25] tidyselect_1.2.0 glue_1.6.2        R6_2.5.1          fansi_1.0.4
[29] rmarkdown_2.21   farver_2.1.1      tidyr_1.3.0       purrr_1.0.1
[33] magrittr_2.0.3   ellipsis_0.3.2    codetools_0.2-19  backports_1.4.1
[37] scales_1.2.1     htmltools_0.5.5   colorspace_2.1-0  labeling_0.4.2
[41] utf8_1.2.3       munsell_0.5.0
```

## 8 Prediction of individual treatment effect using data from multiple studies

Orestis Efthimiou (Institute of Social and Preventive Medicine (ISPM))

In this chapter, we discuss statistical methods for developing models to predict patient-level treatment effects using data from multiple randomized and non-randomized studies. We will first present prediction models that assume a constant treatment effect and discuss how to address heterogeneity in baseline risk. Subsequently, we will discuss approaches that allow for treatment effect modification by adopting two different approaches in an IPD-MA context, namely the risk modelling and the effect modelling approach. For both approaches, we will first discuss how to combine IPD from RCTs comparing the same two treatments. We will then discuss how these methods can be extended to include randomized data from multiple treatments, real-world data, and published aggregate data. We will discuss statistical software to implement these approaches and provide example code as supporting information. Real examples will be used throughout to illustrate the main methods.

We hereby provide code for estimating patient-level treatment effects for the case when we have patient-level data from multiple randomized trials.

### 8.0.1 Example of a continuous outcome

#### 8.0.1.1 Setup

We start by simulating an artificial dataset using the R package **bipd**:

```
library(bipd)
ds <- generate_ipdma_example(type = "continuous")
```

Let us have a look at the dataset:

```
head(ds)
```

Table 8.1: The simulated dataset with a continuous outcome

|                   | 0                     | 1                     | Overall               |
|-------------------|-----------------------|-----------------------|-----------------------|
|                   | (N=280)               | (N=320)               | (N=600)               |
| <b>z1</b>         |                       |                       |                       |
| Mean (SD)         | 0.00453 (1.05)        | 0.0842 (0.996)        | 0.0470 (1.02)         |
| Median [Min, Max] | 0.0424 [-3.32, 3.60]  | 0.0932 [-2.42, 2.99]  | 0.0670 [-3.32, 3.60]  |
| <b>z2</b>         |                       |                       |                       |
| Mean (SD)         | -0.0129 (1.02)        | -0.0320 (0.994)       | -0.0231 (1.01)        |
| Median [Min, Max] | -0.0189 [-2.57, 3.43] | -0.0832 [-2.95, 2.92] | -0.0351 [-2.95, 3.43] |
| <b>studyid</b>    |                       |                       |                       |
| 1                 | 46 (16.4%)            | 54 (16.9%)            | 100 (16.7%)           |
| 2                 | 51 (18.2%)            | 49 (15.3%)            | 100 (16.7%)           |
| 3                 | 47 (16.8%)            | 53 (16.6%)            | 100 (16.7%)           |
| 4                 | 50 (17.9%)            | 50 (15.6%)            | 100 (16.7%)           |
| 5                 | 40 (14.3%)            | 60 (18.8%)            | 100 (16.7%)           |
| 6                 | 46 (16.4%)            | 54 (16.9%)            | 100 (16.7%)           |

|   | studyid | treat | z1         | z2         | y  |
|---|---------|-------|------------|------------|----|
| 1 | 1       | 0     | 0.9753016  | -0.2599767 | 11 |
| 2 | 1       | 1     | 0.5335720  | -0.5522604 | 6  |
| 3 | 1       | 0     | -0.9011067 | 1.5785622  | 11 |
| 4 | 1       | 0     | -1.3821428 | 0.9132537  | 11 |
| 5 | 1       | 0     | 0.5272515  | 0.6478884  | 11 |
| 6 | 1       | 0     | 0.7369785  | 0.9802165  | 11 |

The simulated dataset contains information on the following variables:

- the trial indicator **studyid**
- the treatment indicator **treat**, which takes the values 0 for control and 1 for active treatment
- two prognostic variables **z1** and **z2**
- the continuous outcome **y**

### 8.0.1.2 Model fitting

We synthesize the evidence using a Bayesian random effects meta-analysis model. The model is given in Equation 16.7 of the book. First we need set up the data and create the model:

```

ipd <- with(ds, ipdma.model.onestage(y = y, study = studyid, treat = treat,
                                     X = cbind(z1, z2),
                                     response = "normal",
                                     shrinkage = "none"),
                                     type="random")

```

The JAGS model can be accessed as follows:

```
ipd$model.JAGS
```

```

function ()
{
  for (i in 1:Np) {
    y[i] ~ dnorm(mu[i], sigma)
    mu[i] <- alpha[studyid[i]] + inprod(beta[], X[i, ]) +
      (1 - equals(treat[i], 1)) * inprod(gamma[], X[i,
      ]) + d[studyid[i], treat[i]]
  }
  sigma ~ dgamma(0.001, 0.001)
  for (j in 1:Nstudies) {
    d[j, 1] <- 0
    d[j, 2] ~ dnorm(delta[2], tau)
  }
  sd ~ dnorm(0, 1)
  T(0, )
  tau <- pow(sd, -2)
  delta[1] <- 0
  delta[2] ~ dnorm(0, 0.001)
  for (j in 1:Nstudies) {
    alpha[j] ~ dnorm(0, 0.001)
  }
  for (k in 1:Ncovariate) {
    beta[k] ~ dnorm(0, 0.001)
  }
  for (k in 1:Ncovariate) {
    gamma[k] ~ dnorm(0, 0.001)
  }
}
<environment: 0x0000024dbefe6c10>

```

We can fit the treatment effect model as follows:

```

samples <- ipd.run(ipd, n.chains = 2, n.iter = 20,
  pars.save = c("alpha", "beta", "delta", "sd", "gamma"))

```

```

Compiling model graph
  Resolving undeclared variables
  Allocating nodes
Graph information:
  Observed stochastic nodes: 600
  Unobserved stochastic nodes: 19
  Total graph size: 6034

```

Initializing model

Here are the estimated model parameters:

```
summary(samples)
```

```

Iterations = 2001:2020
Thinning interval = 1
Number of chains = 2
Sample size per chain = 20

```

1. Empirical mean and standard deviation for each variable,  
plus standard error of the mean:

|          | Mean    | SD      | Naive SE | Time-series SE |
|----------|---------|---------|----------|----------------|
| alpha[1] | 10.9627 | 0.05398 | 0.008535 | 0.011004       |
| alpha[2] | 7.9897  | 0.05497 | 0.008692 | 0.008720       |
| alpha[3] | 10.4637 | 0.05789 | 0.009153 | 0.010889       |
| alpha[4] | 9.6431  | 0.04469 | 0.007067 | 0.007159       |
| alpha[5] | 12.9361 | 0.07083 | 0.011199 | 0.015200       |
| alpha[6] | 15.9006 | 0.05371 | 0.008493 | 0.017285       |
| beta[1]  | 0.2052  | 0.01704 | 0.002694 | 0.002532       |
| beta[2]  | 0.2901  | 0.02161 | 0.003418 | 0.005191       |
| delta[1] | 0.0000  | 0.00000 | 0.000000 | 0.000000       |
| delta[2] | -2.3707 | 0.80802 | 0.127759 | 0.106608       |
| gamma[1] | -0.5404 | 0.02647 | 0.004186 | 0.004095       |
| gamma[2] | 0.5927  | 0.03136 | 0.004958 | 0.006968       |
| sd       | 2.0794  | 0.41767 | 0.066040 | 0.119153       |



2. Quantiles for each variable:

|          | 2.5%    | 25%     | 50%     | 75%     | 97.5%   |
|----------|---------|---------|---------|---------|---------|
| alpha[1] | 10.8564 | 10.9210 | 10.9737 | 11.0017 | 11.0558 |
| alpha[2] | 7.8940  | 7.9466  | 7.9908  | 8.0393  | 8.0704  |
| alpha[3] | 10.3824 | 10.4262 | 10.4575 | 10.4981 | 10.5943 |
| alpha[4] | 9.5589  | 9.6231  | 9.6441  | 9.6700  | 9.7093  |
| alpha[5] | 12.8068 | 12.8937 | 12.9368 | 12.9683 | 13.0748 |
| alpha[6] | 15.8038 | 15.8681 | 15.9028 | 15.9361 | 15.9894 |
| beta[1]  | 0.1691  | 0.1966  | 0.2045  | 0.2166  | 0.2369  |
| beta[2]  | 0.2520  | 0.2807  | 0.2923  | 0.3027  | 0.3241  |
| delta[1] | 0.0000  | 0.0000  | 0.0000  | 0.0000  | 0.0000  |
| delta[2] | -4.1413 | -2.7365 | -2.3399 | -1.9803 | -1.0305 |
| gamma[1] | -0.5852 | -0.5564 | -0.5362 | -0.5219 | -0.5008 |
| gamma[2] | 0.5390  | 0.5688  | 0.5904  | 0.6129  | 0.6539  |
| sd       | 1.3300  | 1.8293  | 2.0270  | 2.3425  | 2.8810  |

### 8.0.1.3 Prediction

We can now predict the individualized treatment effect for a new patient with covariate values  $z_1=1$  and  $z_2=0.5$ .

```
round(treatment.effect(ipd, samples, newpatient = c(z1 = 1, z2 = 0.5)), 2)
```

```
0.025    0.5 0.975  
-4.36 -2.53 -1.24
```

We can also predict treatment benefit for all patients in the sample, and look at the distribution of predicted benefit.

```
library(dplyr)  
library(ggplot2)  
  
ds <- ds %>% mutate(benefit = NA)  
  
for (i in seq(nrow(ds))) {  
  newpat <- as.matrix(ds[i, c("z1", "z2")])  
  ds$benefit[i] <- treatment.effect(ipd, samples, newpatient = newpat)["0.5"]  
}
```

```
ggplot(ds, aes(x = benefit)) + geom_histogram() + facet_wrap(~studyid) +
  xlab("Predicted treatment benefit")
```

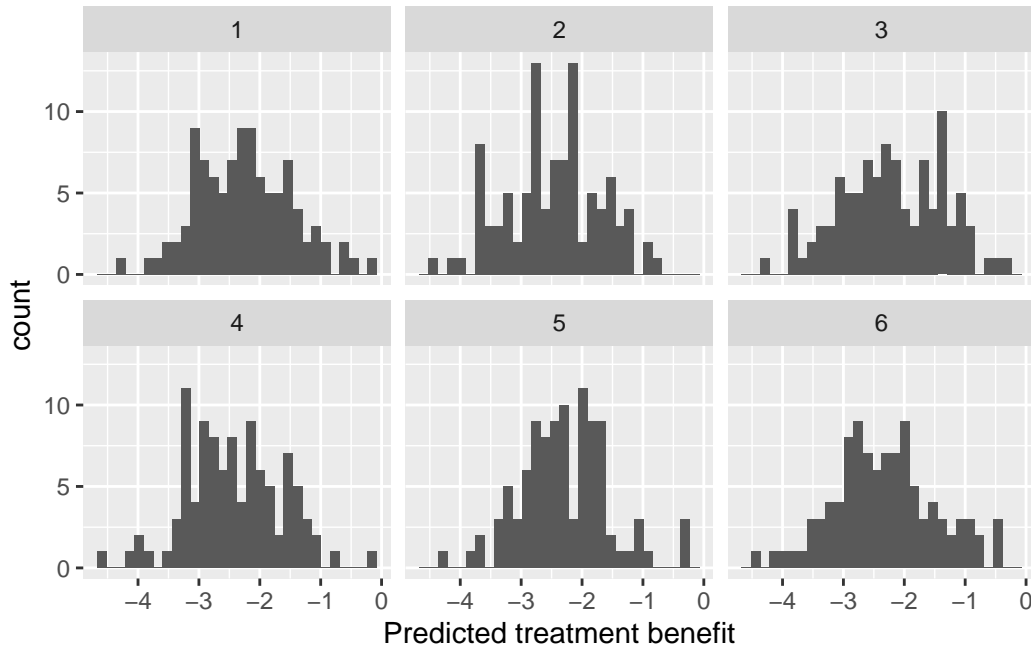


Figure 8.1: Distribution of predicted treatment benefit in each trial

#### 8.0.1.4 Penalization

Let us repeat the analysis, but this time while penalizing the treatment-covariate coefficients using a Bayesian LASSO prior.

```
ipd <- with(ds, ipdma.model.onestage(y = y, study = studyid,
  treat = treat,
  X = cbind(z1, z2),
  response = "normal",
  shrinkage = "laplace"),
  type = "random")

samples <- ipd.run(ipd, n.chains = 2, n.iter = 20,
  pars.save = c("alpha", "beta", "delta", "sd", "gamma"))
```

Compiling model graph

```
Resolving undeclared variables
Allocating nodes
Graph information:
  Observed stochastic nodes: 600
  Unobserved stochastic nodes: 20
  Total graph size: 6039
```

```
Initializing model
```

```
round(treatment.effect(ipd, samples, newpatient = c(1,0.5)), 2)
```

```
0.025    0.5 0.975
-4.42 -2.93 -1.55
```

## 8.0.2 Example of a binary outcome

### 8.0.2.1 Setup

We now present the case of a binary outcome. We first generate a dataset as before, using the **bipd** package.

```
ds2 <- generate_ipdma_example(type = "binary")
head(ds2)
```

|   | studyid | treat | w1          | w2          | y |
|---|---------|-------|-------------|-------------|---|
| 1 | 1       | 0     | 2.26079432  | 0.08270796  | 0 |
| 2 | 1       | 1     | -0.87905267 | 0.07818534  | 1 |
| 3 | 1       | 1     | 0.84648407  | -0.68557300 | 0 |
| 4 | 1       | 1     | -0.07243274 | -0.21915053 | 0 |
| 5 | 1       | 0     | -1.39887558 | -1.18472380 | 1 |
| 6 | 1       | 0     | 1.13010890  | 1.01019519  | 0 |

The simulated dataset contains information on the following variables:

- the trial indicator **studyid**
- the treatment indicator **treat**, which takes the values 0 for control and 1 for active treatment
- two prognostic variables **w1** and **w2**
- the binary outcome **y**

Table 8.2: The simulated dataset with a binary outcome

|                   | 0                      | 1                    | Overall                |
|-------------------|------------------------|----------------------|------------------------|
|                   | (N=281)                | (N=319)              | (N=600)                |
| <b>w1</b>         |                        |                      |                        |
| Mean (SD)         | 0.00132 (1.06)         | 0.0394 (1.02)        | 0.0216 (1.04)          |
| Median [Min, Max] | -0.00704 [-3.50, 2.81] | 0.0208 [-3.53, 3.28] | -0.00250 [-3.53, 3.28] |
| <b>w2</b>         |                        |                      |                        |
| Mean (SD)         | 0.0569 (1.05)          | 0.0536 (0.989)       | 0.0551 (1.02)          |
| Median [Min, Max] | 0.0533 [-3.20, 3.14]   | 0.0396 [-2.61, 2.94] | 0.0452 [-3.20, 3.14]   |
| <b>studyid</b>    |                        |                      |                        |
| 1                 | 54 (19.2%)             | 46 (14.4%)           | 100 (16.7%)            |
| 2                 | 48 (17.1%)             | 52 (16.3%)           | 100 (16.7%)            |
| 3                 | 48 (17.1%)             | 52 (16.3%)           | 100 (16.7%)            |
| 4                 | 46 (16.4%)             | 54 (16.9%)           | 100 (16.7%)            |
| 5                 | 43 (15.3%)             | 57 (17.9%)           | 100 (16.7%)            |
| 6                 | 42 (14.9%)             | 58 (18.2%)           | 100 (16.7%)            |

### 8.0.2.2 Model fitting

We use a Bayesian random effects model with binomial likelihood. This is similar to the model 16.7 of the book, but with a Binomial likelihood, i.e.

$$y_{ij} \sim \text{Binomial}(\pi_{ij})$$

$$\text{logit}(\pi_{ij}) = a_j + \delta_j t_{ij} + \sum_{l=1}^L \beta_l x_{lj} + \sum_{l=1}^L \gamma_l x_{lj} t_{ij}$$

The remaining of the model is as in the book. We can penalize the estimated parameters for effect modification ( $\gamma$ 's), using a Bayesian LASSO. We can do this using again the *bipd* package:

```
ipd2 <- with(ds2, ipdma.model.onestage(y = y, study = studyid, treat = treat,
                                     X = cbind(w1, w2),
                                     response = "binomial",
                                     shrinkage = "laplace"),
            type="random", hy.prior = list("dunif", 0, 1))

ipd2$model.JAGS
```

```

function ()
{
  for (i in 1:Np) {
    y[i] ~ dbern(p[i])
    logit(p[i]) <- alpha[studyid[i]] + inprod(beta[], X[i,
      ]) + (1 - equals(treat[i], 1)) * inprod(gamma[],
        X[i, ]) + d[studyid[i], treat[i]]
  }
  for (j in 1:Nstudies) {
    d[j, 1] <- 0
    d[j, 2] ~ dnorm(delta[2], tau)
  }
  sd ~ dnorm(0, 1)
  T(0, )
  tau <- pow(sd, -2)
  delta[1] <- 0
  delta[2] ~ dnorm(0, 0.001)
  for (j in 1:Nstudies) {
    alpha[j] ~ dnorm(0, 0.001)
  }
  for (k in 1:Ncovariate) {
    beta[k] ~ dnorm(0, 0.001)
  }
  tt <- lambda
  lambda <- pow(lambda.inv, -1)
  lambda.inv ~ dunif(0, 5)
  for (k in 1:Ncovariate) {
    gamma[k] ~ ddexp(0, tt)
  }
}
<environment: 0x000001c505248b20>

samples <- ipd.run(ipd2, n.chains = 2, n.iter = 20,
  pars.save = c("alpha", "beta", "delta", "sd", "gamma"))

```

```

Compiling model graph
  Resolving undeclared variables
  Allocating nodes
Graph information:
  Observed stochastic nodes: 600
  Unobserved stochastic nodes: 19

```

Total graph size: 6637

Initializing model

```
summary(samples)
```

Iterations = 2001:2020

Thinning interval = 1

Number of chains = 2

Sample size per chain = 20

1. Empirical mean and standard deviation for each variable,  
plus standard error of the mean:

|          | Mean      | SD      | Naive SE | Time-series SE |
|----------|-----------|---------|----------|----------------|
| alpha[1] | 0.314409  | 0.23693 | 0.03746  | 0.08131        |
| alpha[2] | 0.415040  | 0.25808 | 0.04081  | 0.03509        |
| alpha[3] | 0.372971  | 0.29496 | 0.04664  | 0.07697        |
| alpha[4] | 0.282879  | 0.24504 | 0.03874  | 0.09724        |
| alpha[5] | 0.309193  | 0.36969 | 0.05845  | 0.09239        |
| alpha[6] | 0.416293  | 0.23513 | 0.03718  | 0.04240        |
| beta[1]  | -0.081624 | 0.09859 | 0.01559  | 0.03202        |
| beta[2]  | -0.001239 | 0.11278 | 0.01783  | 0.03134        |
| delta[1] | 0.000000  | 0.00000 | 0.00000  | 0.00000        |
| delta[2] | 0.163257  | 0.21499 | 0.03399  | 0.07353        |
| gamma[1] | -0.026317 | 0.09577 | 0.01514  | 0.02762        |
| gamma[2] | 0.053277  | 0.13893 | 0.02197  | 0.02543        |
| sd       | 0.212883  | 0.16121 | 0.02549  | 0.03602        |

2. Quantiles for each variable:

|          | 2.5%     | 25%      | 50%      | 75%      | 97.5%  |
|----------|----------|----------|----------|----------|--------|
| alpha[1] | -0.23398 | 0.21377  | 0.26321  | 0.43235  | 0.8062 |
| alpha[2] | -0.03458 | 0.27748  | 0.40672  | 0.60923  | 0.8158 |
| alpha[3] | -0.13235 | 0.21117  | 0.35861  | 0.53537  | 1.0240 |
| alpha[4] | -0.16872 | 0.13181  | 0.26840  | 0.40272  | 0.7910 |
| alpha[5] | -0.31400 | 0.01581  | 0.39064  | 0.55050  | 0.8962 |
| alpha[6] | 0.01672  | 0.28265  | 0.41222  | 0.55848  | 0.9974 |
| beta[1]  | -0.23068 | -0.16032 | -0.09926 | -0.04024 | 0.1046 |
| beta[2]  | -0.21747 | -0.04087 | 0.01067  | 0.07342  | 0.1670 |

```
delta[1] 0.00000 0.00000 0.00000 0.00000 0.00000
delta[2] -0.24775 -0.01175 0.20478 0.30920 0.4467
gamma[1] -0.20439 -0.07810 -0.01325 0.01843 0.1247
gamma[2] -0.15807 -0.01805 0.02882 0.11297 0.4175
sd        0.05884 0.09855 0.15546 0.27606 0.6014
```

```
round(treatment.effect(ipd2, samples, newpatient = c(w1= 1.6, w2 = 1.3)), 2)
```

```
0.025    0.5 0.975
0.71    1.16 2.51
```

## 8.1 Estimating heterogeneous treatment effects in network meta-analysis

### 8.1.1 Example of a continuous outcome

#### 8.1.1.1 Setup

We use again the bipd package to simulate a dataset:

```
ds3 <- generate_ipdnma_example(type = "continuous")
head(ds3)
```

```
studyid treat      z1      z2 y
1      1     1 0.8389580 -0.4623191 11
2      1     1 1.0885397 0.6771985 11
3      1     1 0.5477005 1.0702080 11
4      1     1 0.3168774 -0.5743271 11
5      1     2 -0.1046093 0.2840399 8
6      1     2 0.5195208 -0.7449863 7
```

Let us look into the data a bit in more detail:

#### 8.1.1.2 Model fitting

We will use the model shown in Equation 16.8 in the book. In addition, we will use Bayesian LASSO to penalize the treatment-covariate interactions.

Table 8.3: The simulated dataset with a continuous outcome

|                   | 1                    | 2                     | 3                    | Overall              |
|-------------------|----------------------|-----------------------|----------------------|----------------------|
|                   | (N=363)              | (N=330)               | (N=307)              | (N=1000)             |
| <b>z1</b>         |                      |                       |                      |                      |
| Mean (SD)         | 0.0989 (0.942)       | 0.0146 (1.02)         | 0.0343 (1.02)        | 0.0512 (0.990)       |
| Median [Min, Max] | 0.141 [-2.86, 2.88]  | -0.0756 [-3.57, 2.87] | 0.0399 [-3.30, 2.86] | 0.0401 [-3.57, 2.88] |
| <b>z2</b>         |                      |                       |                      |                      |
| Mean (SD)         | 0.0297 (1.07)        | 0.0740 (1.07)         | 0.0457 (0.951)       | 0.0492 (1.03)        |
| Median [Min, Max] | 0.0676 [-2.88, 2.87] | 0.0709 [-2.58, 3.08]  | 0.0669 [-2.19, 3.03] | 0.0672 [-2.88, 3.08] |
| <b>studyid</b>    |                      |                       |                      |                      |
| 1                 | 53 (14.6%)           | 47 (14.2%)            | 0 (0%)               | 100 (10.0%)          |
| 2                 | 62 (17.1%)           | 38 (11.5%)            | 0 (0%)               | 100 (10.0%)          |
| 3                 | 50 (13.8%)           | 50 (15.2%)            | 0 (0%)               | 100 (10.0%)          |
| 4                 | 48 (13.2%)           | 0 (0%)                | 52 (16.9%)           | 100 (10.0%)          |
| 5                 | 54 (14.9%)           | 0 (0%)                | 46 (15.0%)           | 100 (10.0%)          |
| 6                 | 0 (0%)               | 58 (17.6%)            | 42 (13.7%)           | 100 (10.0%)          |
| 7                 | 0 (0%)               | 47 (14.2%)            | 53 (17.3%)           | 100 (10.0%)          |
| 8                 | 35 (9.6%)            | 29 (8.8%)             | 36 (11.7%)           | 100 (10.0%)          |
| 9                 | 38 (10.5%)           | 24 (7.3%)             | 38 (12.4%)           | 100 (10.0%)          |
| 10                | 23 (6.3%)            | 37 (11.2%)            | 40 (13.0%)           | 100 (10.0%)          |



```

ipd3 <- with(ds3, ipdnma.model.onestage(y = y, study = studyid, treat = treat,
                                         X = cbind(z1, z2),
                                         response = "normal",
                                         shrinkage = "laplace",
                                         type = "random"))

```

```

ipd3$model.JAGS

```

```

function ()
{
  for (i in 1:Np) {
    y[i] ~ dnorm(mu[i], sigma)
    mu[i] <- alpha[studyid[i]] + inprod(beta[], X[i, ]) +
      inprod(gamma[treat[i], ], X[i, ]) + d[studyid[i],
      treatment.arm[i]]
  }
  sigma ~ dgamma(0.001, 0.001)
  for (i in 1:Nstudies) {
    w[i, 1] <- 0
    d[i, 1] <- 0
    for (k in 2:na[i]) {
      d[i, k] ~ dnorm(mdelta[i, k], tau[i, k])
      mdelta[i, k] <- delta[t[i, k]] - delta[t[i, 1]] +
        sw[i, k]
      tau[i, k] <- tau * 2 * (k - 1)/k
      w[i, k] <- d[i, k] - delta[t[i, k]] + delta[t[i,
        1]]
      sw[i, k] <- sum(w[i, 1:(k - 1)])/(k - 1)
    }
  }
  sd ~ dnorm(0, 1)
  T(0, )
  tau <- pow(sd, -2)
  delta[1] <- 0
  for (k in 2:Ntreat) {
    delta[k] ~ dnorm(0, 0.001)
  }
  for (j in 1:Nstudies) {
    alpha[j] ~ dnorm(0, 0.001)
  }
  for (k in 1:Ncovariate) {
    beta[k] ~ dnorm(0, 0.001)
  }
}

```

```

lambda[1] <- 0
lambda.inv[1] <- 0
for (m in 2:Ntreat) {
  tt[m] <- lambda[m] * sigma
  lambda[m] <- pow(lambda.inv[m], -1)
  lambda.inv[m] ~ dunif(0, 5)
}
for (k in 1:Ncovariate) {
  gamma[1, k] <- 0
  for (m in 2:Ntreat) {
    gamma[m, k] ~ ddexp(0, tt[m])
  }
}
}
<environment: 0x000001c505d81000>

```

```

samples <- ipd.run(ipd3, n.chains = 2, n.iter = 20,
  pars.save = c("alpha", "beta", "delta", "sd", "gamma"))

```

Compiling model graph  
 Resolving undeclared variables  
 Allocating nodes  
 Graph information:  
 Observed stochastic nodes: 1000  
 Unobserved stochastic nodes: 35  
 Total graph size: 10141

Initializing model

```
summary(samples)
```

Iterations = 2001:2020  
 Thinning interval = 1  
 Number of chains = 2  
 Sample size per chain = 20

1. Empirical mean and standard deviation for each variable,  
 plus standard error of the mean:

|            | Mean    | SD      | Naive SE | Time-series SE |
|------------|---------|---------|----------|----------------|
| alpha[1]   | 11.0211 | 0.04862 | 0.007687 | 0.010929       |
| alpha[2]   | 8.0023  | 0.03967 | 0.006272 | 0.010361       |
| alpha[3]   | 10.4812 | 0.04786 | 0.007567 | 0.007228       |
| alpha[4]   | 9.6340  | 0.04152 | 0.006564 | 0.010433       |
| alpha[5]   | 12.8820 | 0.04227 | 0.006683 | 0.006530       |
| alpha[6]   | 13.2677 | 0.04441 | 0.007023 | 0.009057       |
| alpha[7]   | 7.5066  | 0.05510 | 0.008712 | 0.015228       |
| alpha[8]   | 11.2471 | 0.04219 | 0.006671 | 0.006427       |
| alpha[9]   | 10.2140 | 0.03848 | 0.006085 | 0.005710       |
| alpha[10]  | 9.1900  | 0.05854 | 0.009256 | 0.011445       |
| beta[1]    | 0.2045  | 0.02841 | 0.004493 | 0.012800       |
| beta[2]    | 0.2951  | 0.02433 | 0.003847 | 0.002858       |
| delta[1]   | 0.0000  | 0.00000 | 0.000000 | 0.000000       |
| delta[2]   | -2.9664 | 0.06247 | 0.009878 | 0.009792       |
| delta[3]   | -1.1461 | 0.05006 | 0.007915 | 0.006894       |
| gamma[1,1] | 0.0000  | 0.00000 | 0.000000 | 0.000000       |
| gamma[2,1] | -0.5682 | 0.03464 | 0.005477 | 0.010041       |
| gamma[3,1] | -0.3085 | 0.04536 | 0.007172 | 0.015676       |
| gamma[1,2] | 0.0000  | 0.00000 | 0.000000 | 0.000000       |
| gamma[2,2] | 0.6212  | 0.04026 | 0.006365 | 0.006315       |
| gamma[3,2] | 0.4465  | 0.03584 | 0.005666 | 0.003887       |
| sd         | 0.1190  | 0.05836 | 0.009227 | 0.017058       |

## 2. Quantiles for each variable:

|            | 2.5%     | 25%      | 50%     | 75%     | 97.5%   |
|------------|----------|----------|---------|---------|---------|
| alpha[1]   | 10.94012 | 10.98910 | 11.0131 | 11.0565 | 11.1000 |
| alpha[2]   | 7.92922  | 7.97699  | 8.0086  | 8.0268  | 8.0752  |
| alpha[3]   | 10.39654 | 10.45390 | 10.4832 | 10.5078 | 10.5795 |
| alpha[4]   | 9.56674  | 9.61476  | 9.6355  | 9.6526  | 9.7022  |
| alpha[5]   | 12.81085 | 12.85152 | 12.8802 | 12.9109 | 12.9630 |
| alpha[6]   | 13.19767 | 13.24110 | 13.2556 | 13.3025 | 13.3532 |
| alpha[7]   | 7.40926  | 7.46692  | 7.5046  | 7.5376  | 7.6142  |
| alpha[8]   | 11.18477 | 11.22359 | 11.2435 | 11.2738 | 11.3282 |
| alpha[9]   | 10.15695 | 10.18448 | 10.2093 | 10.2381 | 10.2860 |
| alpha[10]  | 9.10389  | 9.14602  | 9.1846  | 9.2398  | 9.2911  |
| beta[1]    | 0.16312  | 0.17901  | 0.2075  | 0.2191  | 0.2582  |
| beta[2]    | 0.25611  | 0.27472  | 0.2952  | 0.3115  | 0.3337  |
| delta[1]   | 0.00000  | 0.00000  | 0.0000  | 0.0000  | 0.0000  |
| delta[2]   | -3.10416 | -3.00805 | -2.9512 | -2.9289 | -2.8775 |
| delta[3]   | -1.22663 | -1.18085 | -1.1591 | -1.1234 | -1.0364 |
| gamma[1,1] | 0.00000  | 0.00000  | 0.0000  | 0.0000  | 0.0000  |

```

gamma[2,1] -0.62775 -0.59366 -0.5748 -0.5421 -0.5051
gamma[3,1] -0.39018 -0.34811 -0.2950 -0.2785 -0.2341
gamma[1,2]  0.00000  0.00000  0.0000  0.0000  0.0000
gamma[2,2]  0.54675  0.59428  0.6157  0.6565  0.6873
gamma[3,2]  0.39304  0.41720  0.4477  0.4738  0.5116
sd          0.02979  0.08112  0.1146  0.1633  0.2254

```

As before, we can use the `treatment.effect()` function of *bipd* to estimate relative effects for new patients.

```
treatment.effect(ipd3, samples, newpatient= c(1,2))
```

```

$`treatment 2`
      0.025      0.5      0.975
-2.482723 -2.330572 -2.200555

```

```

$`treatment 3`
      0.025      0.5      0.975
-0.7371516 -0.5980373 -0.4444616

```

This gives us the relative effects for all treatments versus the reference. To obtain relative effects between active treatments we need some more coding:

```

samples.all=data.frame(rbind(samples[[1]], samples[[2]]))
newpatient= c(1,2)
newpatient <- (newpatient - ipd3$scale_mean)/ipd3$scale_sd

median(
  samples.all$delta.2.+samples.all$gamma.2.1.*
  newpatient[1]+samples.all$gamma.2.2.*newpatient[2]
-
  (samples.all$delta.3.+samples.all$gamma.3.1.*newpatient[1]+
  samples.all$gamma.3.2.*newpatient[2])
)

```

```
[1] -1.749739
```

```

quantile(samples.all$delta.2.+samples.all$gamma.2.1.*
  newpatient[1]+samples.all$gamma.2.2.*newpatient[2]
-(samples.all$delta.3.+samples.all$gamma.3.1.*newpatient[1]+

```

```

      samples.all$gamma.3.2.*newpatient[2])
, probs = 0.025)

```

```

      2.5%
-1.919473

```

```

quantile(samples.all$delta.2.+samples.all$gamma.2.1.*
      newpatient[1]+samples.all$gamma.2.2.*newpatient[2]
-(samples.all$delta.3.+samples.all$gamma.3.1.*newpatient[1]+
      samples.all$gamma.3.2.*newpatient[2])
, probs = 0.975)

```

```

      97.5%
-1.582467

```

## 8.1.2 Modeling patient-level relative effects using randomized and observational evidence for a network of treatments

We will now follow Chapter 16.3.5 from the book. In this analysis we will not use penalization, and we will assume fixed effects. For an example with penalization and random effects, see part 2 of this vignette.

### 8.1.2.1 Setup

We generate a very simple dataset of three studies comparing three treatments. We will assume 2 RCTs and 1 non-randomized trial:

```

ds4 <- generate_ipdnma_example(type = "continuous")
ds4 <- ds4 %>% filter(studyid %in% c(1,4,10)) %>%
  mutate(studyid = factor(studyid)) %>%
  recode_factor(
    "1" = "1",
    "4" = "2",
    "10" = "3"),
  design = ifelse(studyid == "3", "nrs", "rct"))

```

The sample size is as follows:

```

          s1 s2 s3
treat A: 50 50 32
treat B: 50  0 34
treat C:  0 50 34

```

### 8.1.2.2 Model fitting

We will use the design-adjusted model, equation 16.9 in the book. We will fit a two-stage fixed effects meta-analysis and we will use a variance inflation factor. The code below is used to specify the analysis of each individual study. Briefly, in each study we adjust the treatment effect for the prognostic factors **z1** and **z2**, as well as their interaction with **treat**.

```
library(rjags)
```

Loading required package: coda

Linked to JAGS 4.3.1

Loaded modules: basemod,bugs

```

first.stage <- "
model{

  for (i in 1:N){
    y[i] ~ dnorm(mu[i], tau)
    mu[i] <- a + inprod(b[], X[i,]) + inprod(c[,treat[i]], X[i,]) + d[treat[i]]
  }
  sigma ~ dunif(0, 5)
  tau <- pow(sigma, -2)

  a ~ dnorm(0, 0.001)

  for(k in 1:Ncovariate){
    b[k] ~ dnorm(0,0.001)
  }

  for(k in 1:Ncovariate){
    c[k,1] <- 0
  }
}

```

```

tauGamma <- pow(sdGamma,-1)
sdGamma ~ dunif(0, 5)

for(k in 1:Ncovariate){
  for(t in 2:Ntreat){
    c[k,t] ~ ddexp(0, tauGamma)
  }
}

d[1] <- 0
for(t in 2:Ntreat){
  d[t] ~ dnorm(0, 0.001)
}
}"

```

Subsequently, we estimate the relative treatment effects in the first (randomized) study comparing treatments A and B:

```

model1.spec <- textConnection(first.stage)
data1 <- with(ds4 %>% filter(studyid == 1),
  list(y = y,
    N = length(y),
    X = cbind(z1,z2),
    treat = treat,
    Ncovariate = 2,
    Ntreat = 2))
jags.m <- jags.model(model1.spec, data = data1, n.chains = 2, n.adapt = 500,
  quiet = TRUE)
params <- c("d", "c")
samps4.1 <- coda.samples(jags.m, params, n.iter = 50)
samps.all.s1 <- data.frame(as.matrix(samps4.1))

samps.all.s1 <- samps.all.s1[, c("c.1.2.", "c.2.2.", "d.2.")]
delta.1 <- colMeans(samps.all.s1)
cov.1 <- var(samps.all.s1)

```

We repeat the analysis for the second (randomized) study comparing treatments A and C:

```

model1.spec <- textConnection(first.stage)
data2 <- with(ds4 %>% filter(studyid == 2),
  list(y = y,

```

```

      N = length(y),
      X = cbind(z1,z2),
      treat = ifelse(treat == 3, 2, treat),
      Ncovariate = 2,
      Ntreat = 2))
jags.m <- jags.model(model1.spec, data = data2, n.chains = 2, n.adapt = 100,
                    quiet = TRUE)
params <- c("d", "c")
samps4.2 <- coda.samples(jags.m, params, n.iter = 50)
samps.all.s2 <- data.frame(as.matrix(samps4.2))
samps.all.s2 <- samps.all.s2[, c("c.1.2.", "c.2.2.", "d.2.")]
delta.2 <- colMeans(samps.all.s2)
cov.2 <- var(samps.all.s2)

```

Finally, we analyze the third (non-randomized) study comparing treatments A, B, and C:

```

model1.spec <- textConnection(first.stage)
data3 <- with(ds4 %>% filter(studyid == 3),
             list(y = y,
                  N = length(y),
                  X = cbind(z1,z2),
                  treat = treat,
                  Ncovariate = 2,
                  Ntreat = 3))
jags.m <- jags.model(model1.spec, data = data3, n.chains = 2, n.adapt = 100,
                    quiet = TRUE)
params <- c("d", "c")
samps4.3 <- coda.samples(jags.m, params, n.iter = 50)
samps.all.s3 <- data.frame(as.matrix(samps4.3))

samps.all.s3 <- samps.all.s3[, c("c.1.2.", "c.2.2.", "d.2.", "c.1.3.",
                                "c.2.3.", "d.3.")]

delta.3 <- colMeans(samps.all.s3)
cov.3 <- var(samps.all.s3)

```

The corresponding treatment effect estimates are depicted below:

We can now fit the second stage of the network meta-analysis:

```

# second stage
second.stage<-
"model{

```



Table 8.4: Treatment effect estimates.

| study   | comparison | estimate | lowerCI | upperCI |
|---------|------------|----------|---------|---------|
| study 1 | B versus A | -0.83    | -0.98   | -0.70   |
| study 2 | C versus A | -0.58    | -0.70   | -0.46   |
| study 3 | B versus A | -0.91    | -1.05   | -0.76   |
| study 3 | C versus A | -0.30    | -0.43   | -0.19   |

```

#likelihood
y1 ~ dmnorm(Mu1, Omega1)
y2 ~ dmnorm(Mu2, Omega2)
y3 ~ dmnorm(Mu3, Omega3*W)

Omega1 <- inverse(cov.1)
Omega2 <- inverse(cov.2)
Omega3 <- inverse(cov.3)

Mu1 <- c(gamma[,1], delta[2])
Mu2 <- c(gamma[,2], delta[3])
Mu3 <- c(gamma[,1], delta[2], gamma[,2], delta[3])

#parameters
for(i in 1:2){
  gamma[i,1] ~ dnorm(0, 0.001)
  gamma[i,2] ~ dnorm(0, 0.001)
}

delta[1] <- 0
delta[2] ~ dnorm(0, 0.001)
delta[3] ~ dnorm(0, 0.001)

}
"
# NMA
model1.spec <- textConnection(second.stage)
data3 <- list(y1 = delta.1, y2 = delta.2, y3 = delta.3,
             cov.1 = cov.1, cov.2 = cov.2, cov.3 = cov.3, W = 0.5)

jags.m <- jags.model(model1.spec, data = data3, n.chains = 2, n.adapt = 50,

```

```

                                quiet = TRUE)
params <- c("delta", "gamma")
samps4.3 <- coda.samples(jags.m, params, n.iter = 50)
summary(samps4.3)

```

```

Iterations = 1:50
Thinning interval = 1
Number of chains = 2
Sample size per chain = 50

```

1. Empirical mean and standard deviation for each variable,  
plus standard error of the mean:

|            | Mean    | SD      | Naive SE | Time-series SE |
|------------|---------|---------|----------|----------------|
| delta[1]   | 0.0000  | 0.00000 | 0.000000 | 0.000000       |
| delta[2]   | -2.9684 | 0.05088 | 0.005088 | 0.005059       |
| delta[3]   | -1.0747 | 0.04815 | 0.004815 | 0.004705       |
| gamma[1,1] | -0.8750 | 0.06060 | 0.006060 | 0.005195       |
| gamma[2,1] | 0.9116  | 0.10571 | 0.010571 | 0.010623       |
| gamma[1,2] | -0.4690 | 0.06124 | 0.006124 | 0.006979       |
| gamma[2,2] | 0.4288  | 0.05039 | 0.005039 | 0.005059       |

2. Quantiles for each variable:

|            | 2.5%    | 25%     | 50%     | 75%     | 97.5%   |
|------------|---------|---------|---------|---------|---------|
| delta[1]   | 0.0000  | 0.0000  | 0.0000  | 0.0000  | 0.0000  |
| delta[2]   | -3.0383 | -3.0004 | -2.9722 | -2.9450 | -2.8924 |
| delta[3]   | -1.1628 | -1.1053 | -1.0767 | -1.0360 | -0.9838 |
| gamma[1,1] | -1.0047 | -0.9145 | -0.8763 | -0.8326 | -0.7571 |
| gamma[2,1] | 0.8048  | 0.8653  | 0.9030  | 0.9291  | 1.0269  |
| gamma[1,2] | -0.5642 | -0.5006 | -0.4608 | -0.4292 | -0.3768 |
| gamma[2,2] | 0.3436  | 0.3947  | 0.4266  | 0.4547  | 0.5415  |

```

# calculate treatment effects
samples.all=data.frame(rbind(samps4.3[[1]], samps4.3[[2]]))
newpatient= c(1,2)

median(
  samples.all$delta.2.+samples.all$gamma.1.1.*newpatient[1]+
  samples.all$gamma.2.1.*newpatient[2]

```

```
)
```

```
[1] -2.03645
```

```
quantile(samples.all$delta.2.+samples.all$gamma.1.1.*newpatient[1]+
          samples.all$gamma.2.1.*newpatient[2]
          , probs = 0.025)
```

```
2.5%
-2.271102
```

```
quantile(samples.all$delta.2.+samples.all$gamma.1.1.*newpatient[1]+
          samples.all$gamma.2.1.*newpatient[2]
          , probs = 0.975)
```

```
97.5%
-1.846155
```

## Version info

This chapter was rendered using the following version of R and its packages:

```
R version 4.2.3 (2023-03-15 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19045)
```

```
Matrix products: default
```

```
locale:
```

```
[1] LC_COLLATE=Dutch_Netherlands.utf8 LC_CTYPE=Dutch_Netherlands.utf8
[3] LC_MONETARY=Dutch_Netherlands.utf8 LC_NUMERIC=C
[5] LC_TIME=Dutch_Netherlands.utf8
```

```
attached base packages:
```

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

```
other attached packages:
```

```
[1] rjags_4-14          coda_0.19-4          kableExtra_1.3.4  ggplot2_3.4.2
[5] bipd_0.3            dplyr_1.1.2          table1_1.4.3
```

loaded via a namespace (and not attached):

```
[1] pillar_1.9.0      compiler_4.2.3      tools_4.2.3        digest_0.6.31
[5] viridisLite_0.4.2 jsonlite_1.8.4      evaluate_0.21      lifecycle_1.0.3
[9] tibble_3.2.1      gtable_0.3.3       lattice_0.21-8     pkgconfig_2.0.3
[13] rlang_1.1.1       cli_3.6.1          rstudioapi_0.14    yaml_2.3.7
[17] mvtnorm_1.1-3     xfun_0.39          fastmap_1.1.1      stringr_1.5.0
[21] xml2_1.3.4        withr_2.5.0        httr_1.4.6         knitr_1.43
[25] systemfonts_1.0.4 generics_0.1.3      vctrs_0.6.2        webshot_0.5.4
[29] grid_4.2.3        tidyselect_1.2.0   svglite_2.1.1      glue_1.6.2
[33] R6_2.5.1          fansi_1.0.4        rmarkdown_2.22     Formula_1.2-5
[37] magrittr_2.0.3    codetools_0.2-19   scales_1.2.1       htmltools_0.5.5
[41] rvest_1.0.3       colorspace_2.1-0   utf8_1.2.3         stringi_1.7.12
[45] munsell_0.5.0
```

## References

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- Siemieniuk, Reed AC, Jessica J Bartoszko, Dena Zeraatkar, Elena Kum, Anila Qasim, Juan Pablo Díaz Martinez, Ariel Izcovich, et al. 2020. “Drug Treatments for Covid-19: Living Systematic Review and Network Meta-Analysis.” *BMJ*, July, m2980. <https://doi.org/10.1136/bmj.m2980>.