Comparative Effectiveness and Personalized Medicine Research Using Real-World Data

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1 Preface

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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 Dealing with missing data

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

2.0.1 Prepare R environment

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

2.0.2 Generating an observational dataset

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

```r
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.

2.0.3 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`

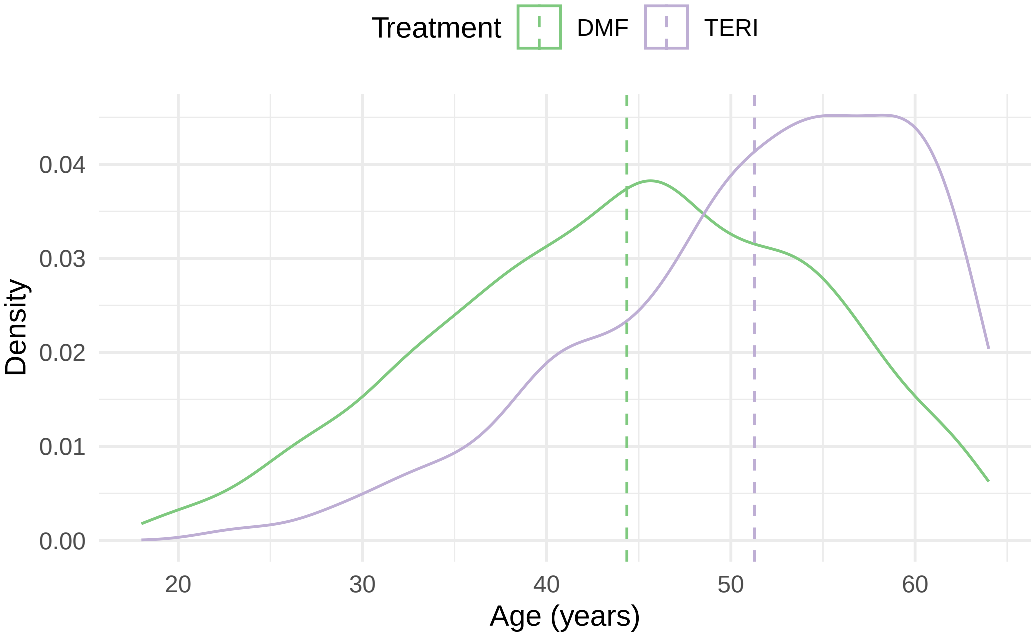


Figure 2.1: Distribution of the EDSS score at each time point

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.

2.1 Analysis of incomplete data

2.1.1 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 2.1: Baseline characteristics of the incomplete dataset.

	DMF	TERI	Overall
	(N=2265)	(N=735)	(N=3000)
Age (years)			
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%)
Female Sex			
Yes	1740 (76.8%)	526 (71.6%)	2266 (75.5%)
No	525 (23.2%)	209 (28.4%)	734 (24.5%)
Efficacy of previous DMT			
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%)
Prior medical costs			
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%)
Number of prior symptoms			
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%)
Number of prior relapses			
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
```

2.1.2 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:

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

```
[1] -0.1554094
```

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

```
[1] 0.2202132
```

2.1.3 Multiple Imputation (across method)

```r
# 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.

```r
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:

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

```
[1] -0.3461563
```

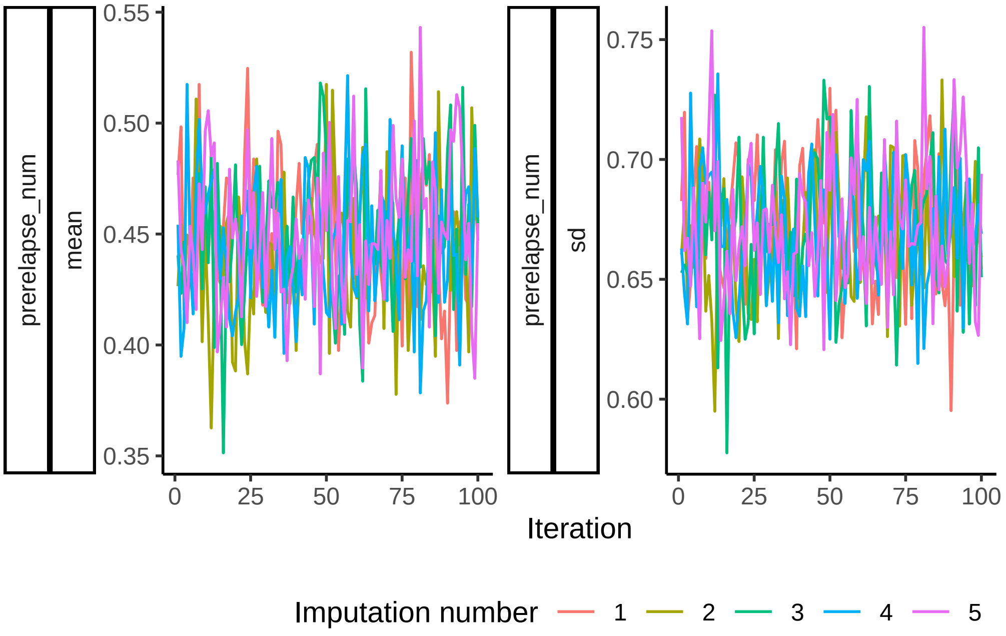
```
# Standard error
(match_mod %>% filter(term == "DMF"))$std.error
```

```
[1] 0.1351187
```

2.2 Convergence checking

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

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

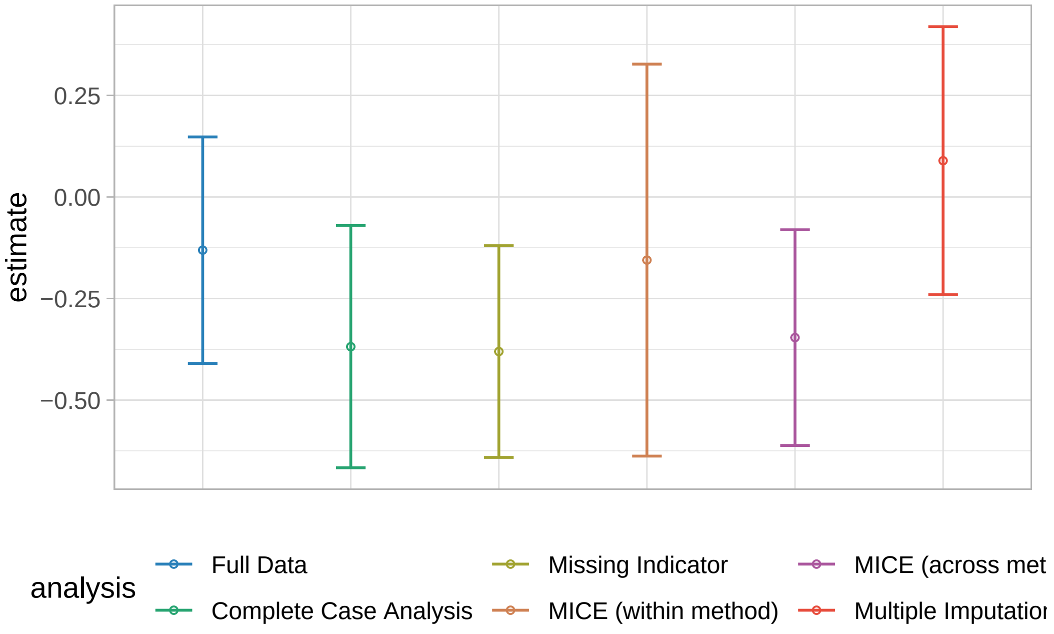


2.3 Results

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 developed 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] ggmice_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
```

3 Confounding adjustment using propensity score methods

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 prevDMTefficacy 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
```

4 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)

5 Estimating the propensity score

5.1 Logistic regression

We sought to restore balance in the distribution of baseline covariates in patients treated with DMT1 (index treatment) and DMT0 (control tratment). 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
```

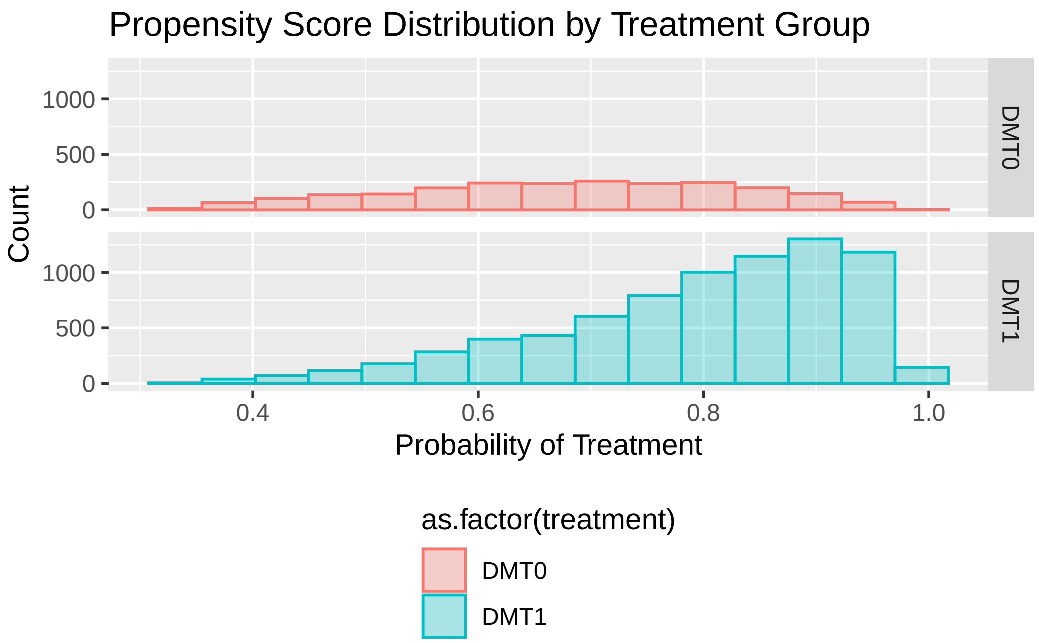
```
(Dispersion parameter for binomial family taken to be 1)

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

Number of Fisher Scoring iterations: 5
```

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

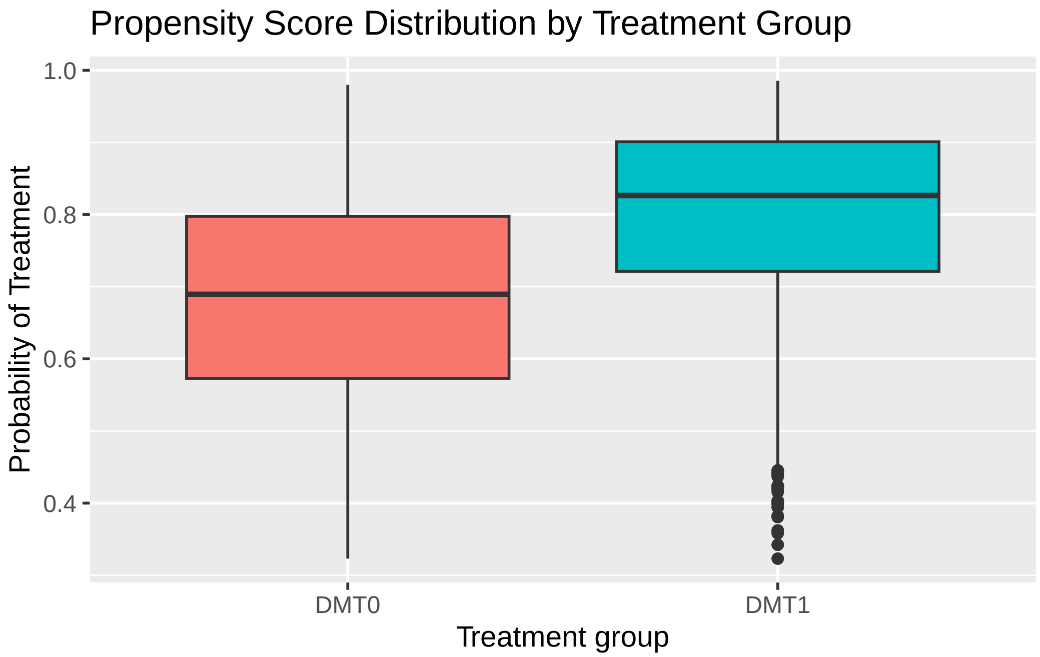
5.2 Assessing overlap

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

```r
# 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 
```

6 Propensity score matching

6.1 1:1 Optimal full matching without replacement

```r
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
```

6.2 Assess balance after matching

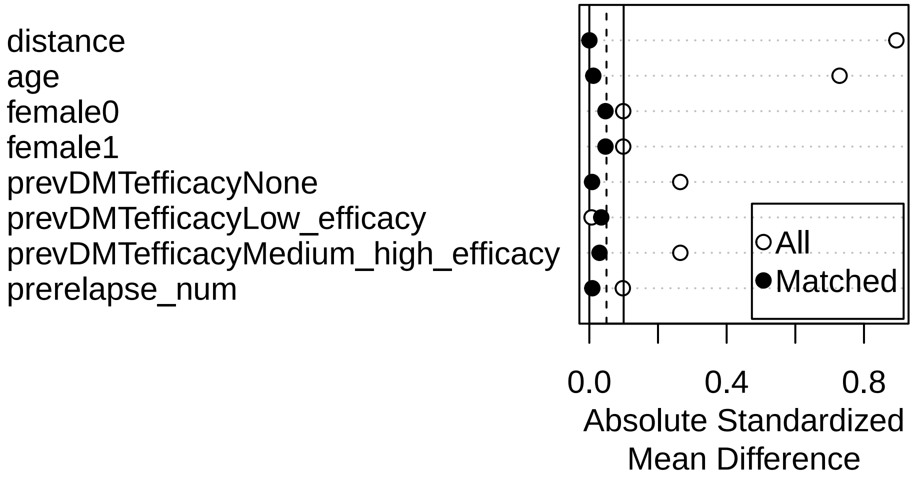
```r
summary(opt)
```

```

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

Summary of Balance for All Data:
```

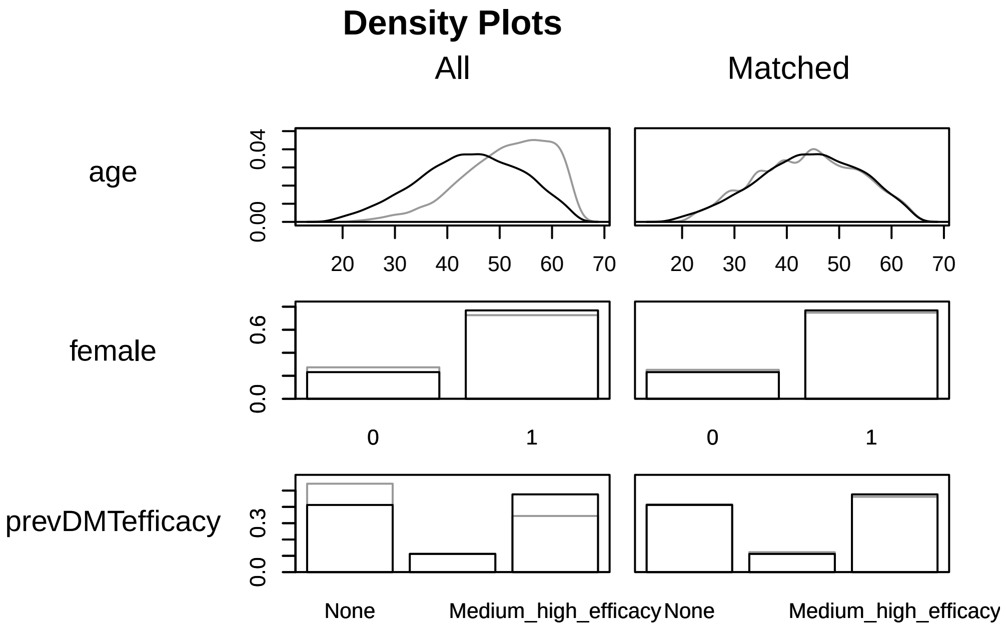
```
                                    Means Treated Means Control Std. Mean Diff.
distance                                   0.7970        0.6795          0.8943
age                                       44.2496       51.3883         -0.7289
female0                                    0.2318        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          0.0001
age                                       44.2496       44.1364          0.0116
female0                                    0.2318        0.2517         -0.0470
female1                                    0.7682        0.7483          0.0470
prevDMTefficacyNone                        0.4118        0.4157         -0.0079
prevDMTefficacyLow_efficacy                0.1114        0.1224         -0.0347
prevDMTefficacyMedium_high_efficacy        0.4768        0.4619          0.0297
prerelapse_num                             0.4595        0.4654         -0.0087
                                    Var. Ratio eCDF Mean eCDF Max
distance                                0.9955    0.0012   0.0116
age                                     1.0161    0.0076   0.0260
female0                                      .    0.0199   0.0199
female1                                      .    0.0199   0.0199
prevDMTefficacyNone                          .    0.0039   0.0039
prevDMTefficacyLow_efficacy                  .    0.0109   0.0109
prevDMTefficacyMedium_high_efficacy          .    0.0148   0.0148
prerelapse_num                          0.9530    0.0057   0.0110
                                    Std. Pair Dist.
distance                                     0.0022
age                                          0.1688
female0                                      0.5149
female1                                      0.5149
```

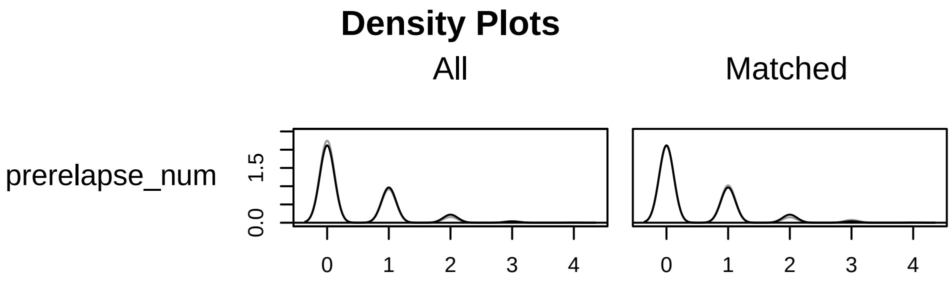
```
prevDMTefficacyNone                        0.1816
prevDMTefficacyLow_efficacy                0.5944
prevDMTefficacyMedium_high_efficacy        0.4731
prerelapse_num                             0.3893

Sample Sizes:
              Control Treated
All           2300.      7700
Matched (ESS)  198.89    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)
```





6.3 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.

```r
# 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 9
  type     term      contrast   estim~1 std.e~2 stati~3  p.value conf.~4 conf.~5
  <chr>    <chr>     <chr>        <dbl>   <dbl>   <dbl>    <dbl>   <dbl>   <dbl>
1 response treatment mean(DMT1~   0.761   0.100    7.59 3.21e-14   0.564   0.958
# ... with abbreviated variable names 1: estimate, 2: std.error, 3: statistic,
#   4: conf.low, 5: conf.high
```

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 0.76 with a 95% confidence interval ranging from 0.56 to 0.96.

7 Propensity score stratification

7.1 Divide sample into quintiles of propensity scores

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

```r
# 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 
```

7.2 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.

7.2.1 Propensity Score Stratum #1

```r
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

7.2.2 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

7.2.3 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

7.2.4 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

7.2.5 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

7.3 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(sapply(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(sapply(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 
```

8 Propensity score weighting

8.1 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.

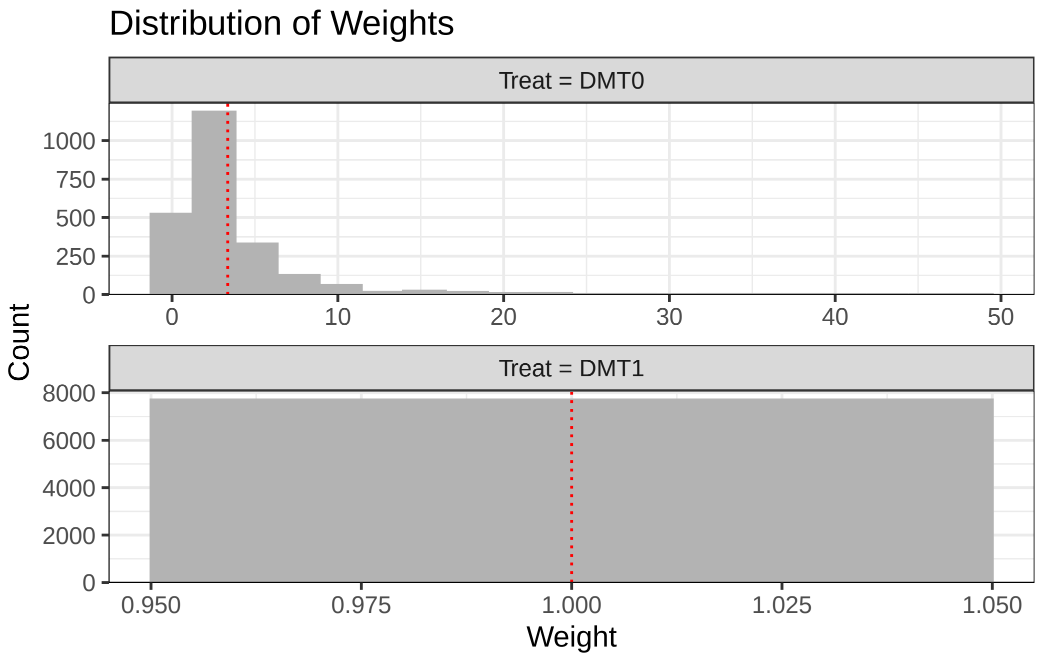
```
library(WeightIt)

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

w.out
```

```
A weightit object
 - method: "ps" (propensity score weighting)
 - 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 5 most extreme weights by group:

         9492    8836    6544    9610    4729
 DMT0 32.1027 32.1027 34.3126 38.1817 48.6856
            6       4       3       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))
```



8.2 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
```

8.3 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.

```r
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
```

```r
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: 0.62; 0.8).

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).

9 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:

```r
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
```

10 Overview

Method	Estimand	Estimate	95% CI (lower)	95% CI (upper)
Optimal full matching	ATT	0.7610138	0.5644807	0.9575469
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

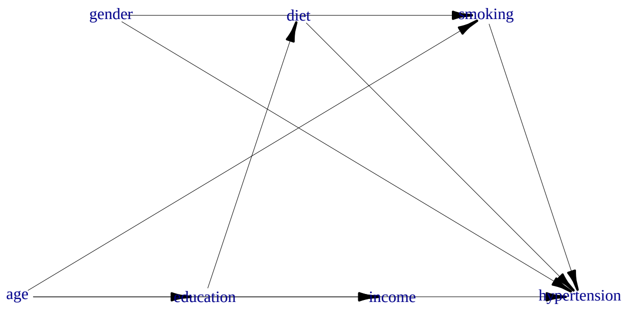
11 Effect Modification Analysis within the Propensity score Framework

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)
plotDAG(Dset)
```



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 12.288936      1         1    1      0       1            1
149   10.400436      1         1    0      0       1            1
10060  2.991820      1         1    0      0       1            0
22220 -4.311952      0         0    0      1       0            1
9979  -6.435549      0         0    0      1       0            1
```

11.1 Effect measure assessment via adding interaction term

Below, we estimate a logistic regression model to assess whether the effect of smoking (the exposure) on hypertension is modified by income. The covariates age and gender are confounders.

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

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

	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

Standard errors: MLE

The interaction term in `results.model` is statistically significant.

Presentation of effect measures

We can generate a summary report from aforementioned effect modification analysis. The table below depicts the adjusted odds ratios for income levels (`high = 0`, and `low = 1`)

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

em.object$dframe[,1:4]
```

```
                                   Measures  Estimates      CI.ll      CI.ul
```

```
1                                 OR00  1.0000000         NA         NA
2                                 OR01  2.9301604  2.6010653  3.3008937
3                                 OR10  0.4832932  0.4068652  0.5740780
4                                 OR11  1.7997639  1.6334908  1.9829619
5 OR(smoking1 on outcome [income0==0]  2.9301604  2.6010653  3.3008937
6 OR(smoking1 on outcome [income0==1]  3.7239584  3.1434919  4.4116118
7                 Multiplicative scale  1.2709060  1.0385052  1.5553143
8                                 RERI -0.6136898 -0.9754808 -0.2905171
```

11.2 Effect measure assessment via stratified approach

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

```
fit.income1 <- glm(hypertension ~ smoking + age + gender,
            family = binomial(link = "logit"),
            data = subset(Obs.Data, income == 1))
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.

```
     Value of income exp(Est.)     2.5%    97.5%   z val.            p
[1,]               1  3.066878 2.707961 3.473366 17.64728 1.067842e-69
[2,]               0  3.590260 3.023124 4.263792 14.57113 4.287200e-48
```

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

```
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)["smoking1"])
```

```
smoking1
3.066878
```

```
# Odds ratio for smoking in individuals with high income
exp(coef(fit.all.int)["smoking1"] + coef(fit.all.int)["income0:smoking1"])
```

```
smoking1
 3.59026
```

11.3 Interaction

Assessment of interaction between smoking and income. We estimate a logistic regression model where

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

An interaction term of smoking and income is added.

```
fit.w.int <- glm(hypertension ~ smoking * income + age + gender +
                   education, family = binomial(link = "logit"),
                 data = Obs.Data)
results.int.model <- summ(fit.w.int, model.info = FALSE, model.fit = FALSE,
                          exp = TRUE)
results.int.model$coeftable
```

```
                exp(Est.)      2.5%     97.5%     z val.             p
(Intercept)     5.6937765 4.5570175 7.1141027 15.3077121  6.791105e-53
smoking1        3.3452459 2.9505339 3.7927612 18.8503257  2.920389e-79
income0         1.0908060 0.8506311 1.3987941  0.6849951  4.933470e-01
age             1.2981524 1.2804814 1.3160673 37.3150071 9.371499e-305
gender          0.5366777 0.4313229 0.6677666 -5.5815569  2.383750e-08
education       0.4233969 0.3502014 0.5118909 -8.8749618  6.995745e-19
smoking1:income0 1.1022535 0.8968615 1.3546825  0.9253438  3.547871e-01
```

The interaction term between income and smoking is, however, not statistically significant.

Table 11.1: **?(caption)**

```
                                Measures Estimates       CI.ll     CI.ul
1                                   OR00 1.0000000          NA        NA
2                                   OR01 1.0908060  0.850631061 1.3987941
3                                   OR10 3.3452459  2.950533888 3.7927612
4                                   OR11 4.0221386  3.287881778 4.9203713
5  OR(income0 on outcome [smoking1==0] 1.0908060  0.850631061 1.3987941
6  OR(income0 on outcome [smoking1==1] 1.2023447  0.997265811 1.4495962
7  OR(smoking1 on outcome [income0==0] 3.3452459  2.950533888 3.7927612
8  OR(smoking1 on outcome [income0==1] 3.6873089  3.112335708 4.3685026
9                  Multiplicative scale 1.1022535  0.896861546 1.3546825
10                                  RERI 0.5860867  0.029944164 1.2657133
11                                    AP 0.1457152 -0.004274684 0.2598376
12                                    SI 1.2405887  1.008364517 1.5262937
```

Presentation of effect measures

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

Summary report from an interaction analysis when investigating association between two exposure variables (smoking and income) and hypertension. Below, `CI.ll` and `CI.ul` depict the lower and upper limits of the 95 percent confidence intervals, `OR11` $= OR_{A=1,M=1}$, `OR10` $= OR_{A=1}$, `OR01` $= OR_{M=1}$ and `OR00` captures the reference.

```r
# 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
```

11.4 Step-by-Step Guideline for Practitioners regarding Implementation

11.4.1 Propensity score matching approaches

Stratified approach with exact matching within subgroups

```r
# For income = 0
require(MatchIt)
set.seed(123)
Obs.Data <- sim(DAG = Dset, n = 5000, rndseed = 123)
```

```
simulating observed dataset from the DAG object
```

```r
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
```

```
# For 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)
```

```
# 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
require(jtools)
fit.nexp.adj.res1 <- summ(fit.income.1,
                          robust = TRUE,
                          cluster = "subclass",
                          model.info = FALSE,
                          model.fit = FALSE,
                          confint = TRUE)
fit.nexp.adj.res0 <- summ(fit.income.0,
                          robust = TRUE,
                          cluster = "subclass",
                          model.info = FALSE,
                          model.fit = FALSE,
                          confint = TRUE)
```

Table 11.2: **?(caption)**

```
     Value of income     Est.         2.5%     97.5%    z val.            p
[1,]               0 3.739945 -37.5789304 45.058820 0.1774046 8.591906e-01
[2,]               1 1.394520   0.9418774  1.847163 6.0383367 1.557109e-09
```

Table 11.3: **?(caption)**

```
  Value of income     Est.      S.E.      2.5%    97.5%   z val.            p
1               0 3.854853 1.0033297 1.8883628 5.821343 3.842060 1.220060e-04
2               1 1.401206 0.2805318 0.8513733 1.951038 4.994819 5.889087e-07
```

Joint approach without exact matching within subgroups

```
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)
```

12 Systematic review and meta-analysis of Real-World Evidence

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

We first load the required packages

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

12.1 Pairwise meta-analysis of clinical trials

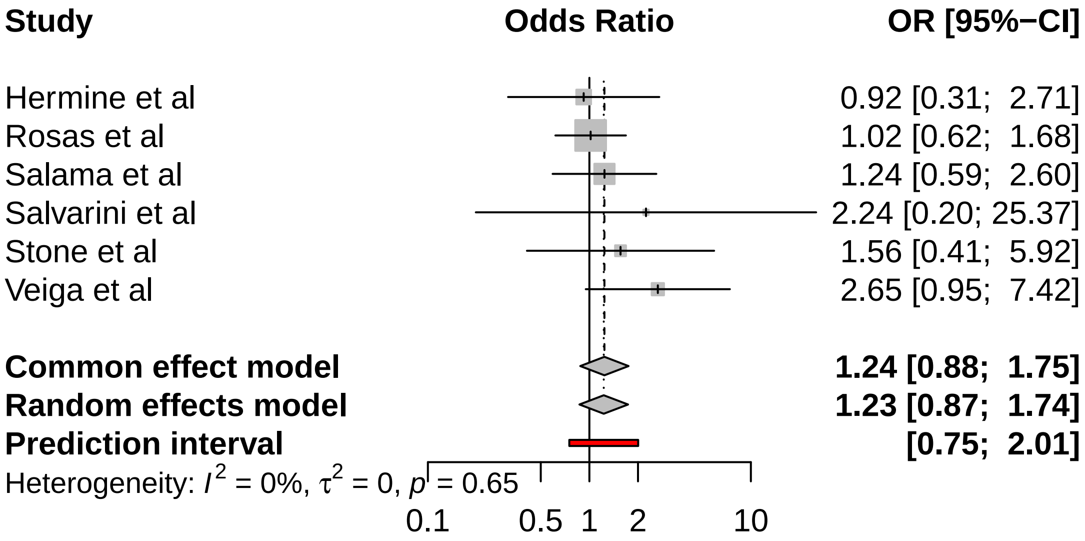
12.1.1 Toculizumab for coronavirus disease 2019

In this example, we consider the results from a systematic literature review of clinical trials investigating any pharmacological in hosptialized 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 comparted toculizumab (`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.

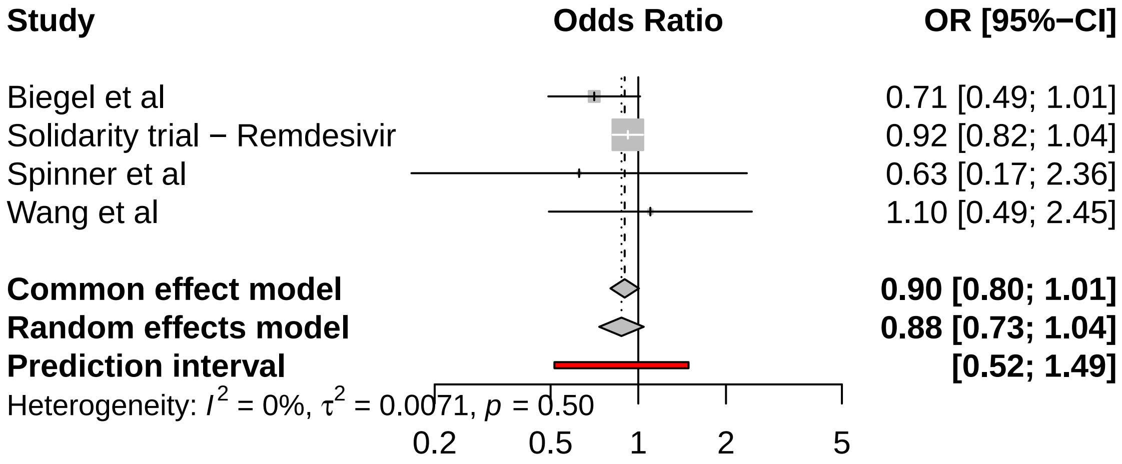
```r
results.TOCI <- metabin(event1,n1,event2,n2,studlab,data=tocilizumab,
                        sm="OR",main="tocilizumab vs standard care",
                        prediction=TRUE)
forest(results.TOCI, leftcols = "studlab", rightcols = "effect.ci")
```



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

12.1.2 Remdesivir for coronavirus disease 2019

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



12.2 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.

12.2.1 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:

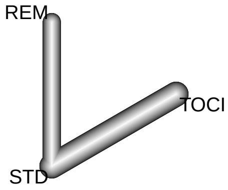


Figure 12.1: Evidence network of the 21 coronavirus-19 trials

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	allst
-0.0819293	0.2483849	Ader	REM	STD	34	414	37	418	0.0	FAL
-0.3483875	0.1851030	Beigel (ACTT-1)	REM	STD	59	541	77	521	0.0	FAL
0.4487619	1.6487159	Broman	TOCI	STD	1	57	0	29	0.5	FAL
-0.6620566	0.7125543	Criner	REM	STD	4	384	4	200	0.0	FAL
0.0170679	0.4904898	Declerq (COV-AID)	TOCI	STD	10	81	9	74	0.0	FAL
-0.4442338	0.1688337	Gordon (REMAP-CAP)	TOCI	STD	83	353	116	358	0.0	FAL

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
```

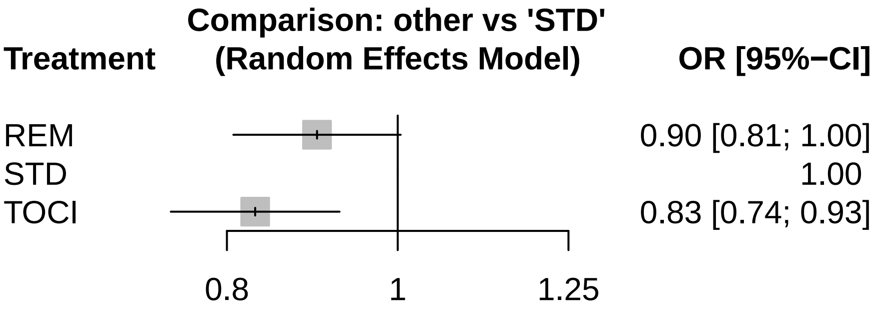
```
Number of studies: k = 20
Number of pairwise comparisons: m = 20
Number of treatments: n = 3
Number of designs: d = 2

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:

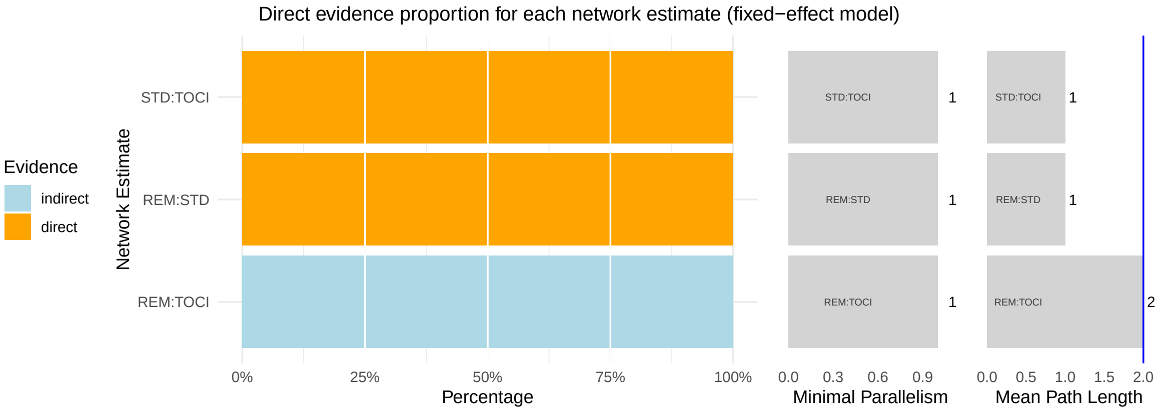
```
netleague(NMA.covid)
```

```
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
```

```r
# 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:

```r
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-β (INTB) (Selvarajan et al. 2022). The corresponding network is displayed below:

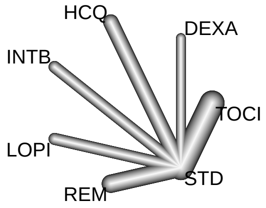


Figure 12.2: Evidence network of the 33 coronavirus-19 trials

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
DEXA 0.8557 [0.7558; 0.9688] -2.46  0.0139
HCQ  1.1809 [0.8934; 1.5610]  1.17  0.2428
INTB 1.1606 [0.9732; 1.3841]  1.66  0.0973
LOPI 1.0072 [0.8906; 1.1392]  0.11  0.9085
REM  0.8983 [0.8014; 1.0070] -1.84  0.0658
```

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

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
```

12.2.2 Pharmacologic treatments for chronic obstructive pulmonary disease

In this example, we consider the resuls 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)
```

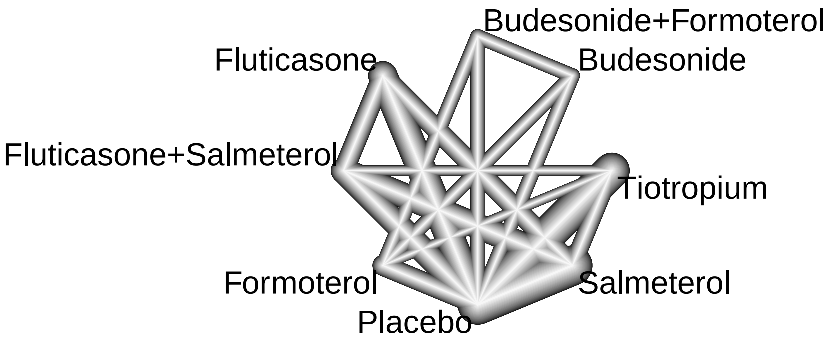
study	year	id	treatment	exac	total
Llewellyn-Jones 1996	1996	1	Fluticasone	0	8
Llewellyn-Jones 1996	1996	1	Placebo	3	8
Boyd 1997	1997	2	Salmeterol	47	229
Boyd 1997	1997	2	Placebo	59	227
Paggiaro 1998	1998	3	Fluticasone	45	142
Paggiaro 1998	1998	3	Placebo	51	139

```r
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
      39 Fluticasone+Salmeterol Salmeterol NA   NA
      39             Salmeterol    Placebo NA   NA
```

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



12.2.3 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 12.4: 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.

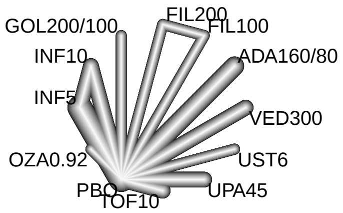


Figure 12.3: Evidence network of 18 trials that contributed efficacy data for induction in bio-naive populations

```r
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):

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

# Exctract 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 developed 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
```

13 Dealing with irregular and informative visits

We first load the required packages

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

13.1 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_
```

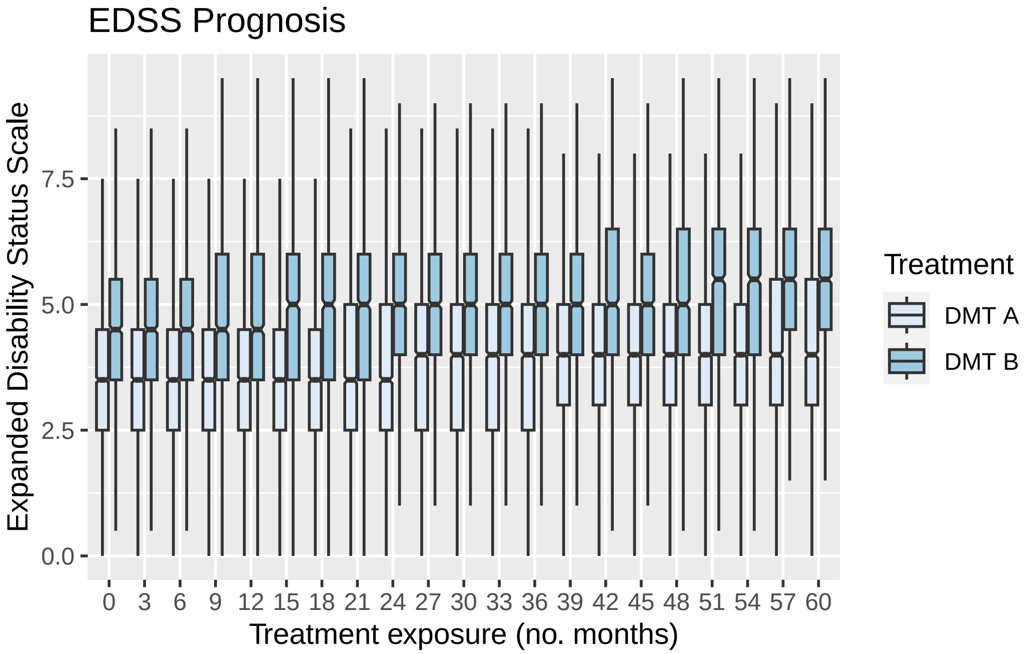


Figure 13.1: Distribution of the EDSS score at each time point

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`.

13.2 Estimation of treatment effect

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

13.2.1 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)
```

13.2.2 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)
```

13.2.3 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

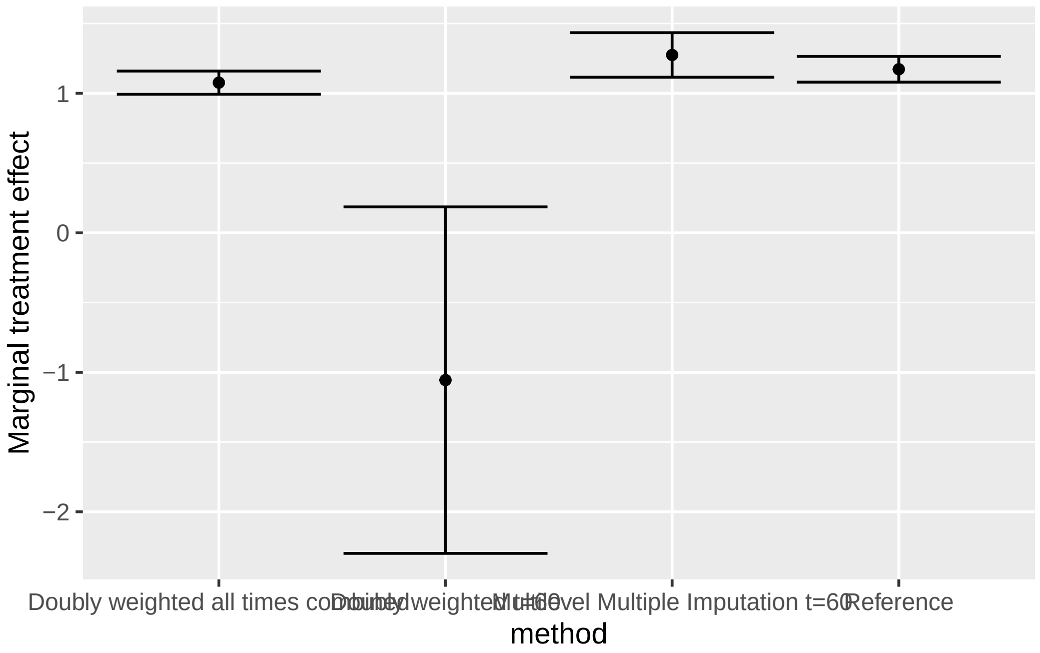
```
# Predict probability of treatment allocation
fitps <- glm(x ~ age + sex + edss, family='binomial', data = dataset_visit)

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

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

13.3.1 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)
```

13.4 Results



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