Advanced Methods in Epidemiology - Causal Inference

Practical Session

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Objectives of practical session:

After this session, the students are able to:

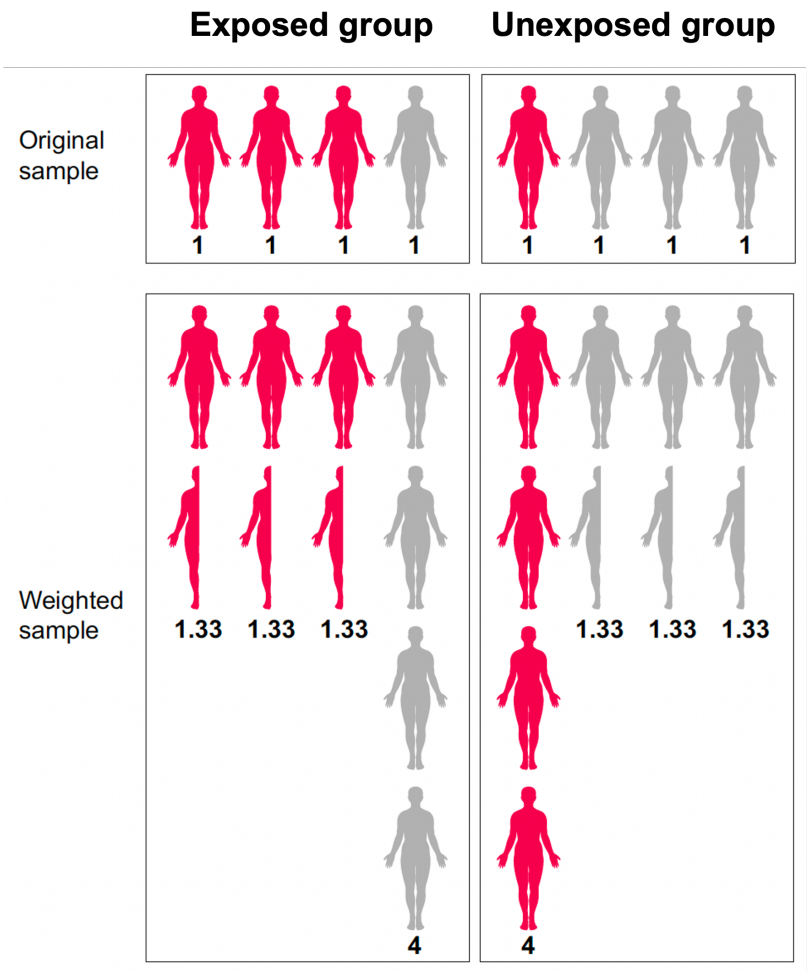
- Understand the applications, strengths and limitations of inverse probability weighting (IPW) for causal inference
- Implement IPW in data analysis of epidemiological studies
- Assess assumptions of IPW method and balance diagnostics

IPW Recap

- Goal: To ensure exchangeability in the study sample
- Steps:

1. Calculate the probability of being exposed (or treated) of each individuals given their characteristics (propensity score)
2. Calculate the weight of each individual as the inverse of the probability of receiving their actual exposure status
3. Apply the weight to the study sample to create a pseudo-population in which all measured confounders are equally distributed across exposure/treatment groups

IPW Recap



Example of balancing the proportion of diabetes individuals (gray figures) between the exposed and unexposed group.

- The probability of being exposed among diabetic individuals is $1/4$

$\Rightarrow$ diabetic individuals in the exposed group receive the weight of $\frac{1}{1/4} = 4 \Rightarrow$ diabetic individuals in the unexposed group receive the weight of $\frac{1}{1-1/4} = 4/3$

Part 1: IPW for point treatment

Right Heart Catheterization Example

Study of Connors *et al.* (1996) on the effectiveness of right heart catheterization (RHC) on mortality in critically ill patients

- ICU patients in 5 hospitals
- Treated group: receiving RHC (2148 patients)
- Control group: not receiving RHC (3551 patients)
- Outcome: mortality
- Confounders: demographics, insurance status, disease diagnoses,...
- Metadata: hbiostat.org/data/repo/rhc.html

Before we start..

Load packages:

```
library(tableone)
library(table1)
library(ipw)
library(sandwich)
library(survey)
library(ggplot2)
library(tidyverse)
```

Import data and view data

```
rhc <- read.csv("rhc.csv")
View(rhc)
```

Imbalance in baseline characteristics

Quick glance at baseline characteristics of treated and control group:

	No RHC	RHC
	(N=3551)	(N=2184)
Age		
Mean (SD)	62 (17)	61 (16)
Sex		
Female	1637 (46.1%)	906 (41.5%)
Male	1914 (53.9%)	1278 (58.5%)
APACHE score		
Mean (SD)	51 (19)	61 (20)
Mean blood pressure		
Mean (SD)	85 (39)	68 (34)
Primary disease		
ARF	1581 (44.5%)	909 (41.6%)
CHF	247 (7.0%)	209 (9.6%)
Cirrhosis	175 (4.9%)	49 (2.2%)
Colon Cancer	6 (0.2%)	1 (0.0%)
Coma	341 (9.6%)	95 (4.3%)
COPD	399 (11.2%)	58 (2.7%)
Lung Cancer	34 (1.0%)	5 (0.2%)
MOSF w/Malignancy	241 (6.8%)	158 (7.2%)
MOSF w/Sepsis	527 (14.8%)	700 (32.1%)

Step 1: Select variables for propensity score model

Good practice

- Include all confounders of exposure-outcome relationship
- Also include all variables that predict the outcome
- Only include variables that are measured before exposure

Do NOT

- Include outcome in the propensity score model
- Use p-values to select variables
- Select variables that only relate to the exposure, but not to the outcome

Step 1: Select variables for propensity score model

Variables to be selected in the RHC example:

- **age**
- **sex**
- **cat1** : primary disease category
- **meanbp1** : Mean blood pressure
- **aps1** : APACHE score

Some data manipulation

Create new dataset with only variables that will be used in our analysis:

```
treatment <- as.numeric(rhc$swang1=='RHC')
died <- as.numeric(rhc$death=='Yes')
age <- rhc$age
female <- as.numeric(rhc$sex=='Female')
ARF <- as.numeric(rhc$cat1=='ARF')
CHF <- as.numeric(rhc$cat1=='CHF')
cirr <- as.numeric(rhc$cat1=='Cirrhosis')
colcan <- as.numeric(rhc$cat1=='Colon Cancer')
coma <- as.numeric(rhc$cat1=='Coma')
COPD <- as.numeric(rhc$cat1=='COPD')
lungcan <- as.numeric(rhc$cat1=='Lung Cancer')
MOSF <- as.numeric(rhc$cat1=='MOSF w/Malignancy')
sepsis <- as.numeric(rhc$cat1=='MOSF w/Sepsis')
meanbp1 <- rhc$meanbp1
apache <- rhc$aps1
```

New dataset:

```
mydata <- as.data.frame(cbind(treatment, died, age, female, ARF, CHF, cirr, colcan, coma,
                              COPD, lungcan, MOSF, sepsis, meanbp1, apache))
View(mydata)
```

Step 2: Calculate propensity score

Fit propensity score model:

- Outcome: treatment assignment
- Predictors: confounders and other study outcome (mortality) predictors

```
psmodel <- glm(treatment ~ age + female + meanbp1 + apache + ARF + CHF + cirr + colcan +
                 coma  + lungcan + MOSF + sepsis,
               family = binomial(link = "logit"))
summary(psmodel)$coefficients
```

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-1.9460154	0.2321291	-8.3833310	0.0000000
age	-0.0030469	0.0017462	-1.7448453	0.0810118
female	-0.1390768	0.0590139	-2.3566784	0.0184392
meanbp1	-0.0075166	0.0008707	-8.6329043	0.0000000
apache	0.0182356	0.0017286	10.5494907	0.0000000
ARF	1.2252931	0.1495511	8.1931395	0.0000000
CHF	1.8905642	0.1735687	10.8923093	0.0000000
cirr	0.4334062	0.2203366	1.9670185	0.0491811
colcan	0.0481566	1.1242894	0.0428329	0.9658347
coma	0.6842545	0.1878333	3.6428820	0.0002696
lungcan	0.1984600	0.5055005	0.3926011	0.6946141
MOSF	1.0177798	0.1807159	5.6319339	0.0000000
sepsis	1.8402456	0.1561589	11.7844413	0.0000000

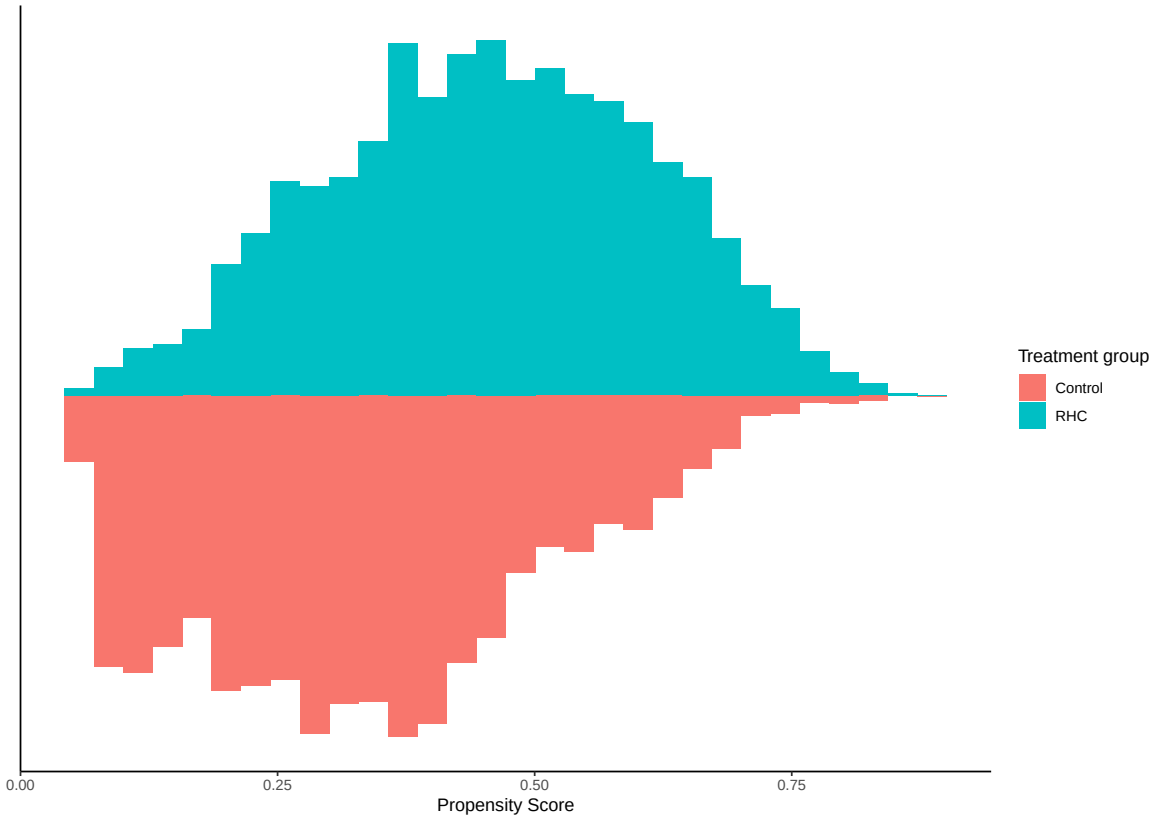
Step 2: Calculate propensity score

Calculate propensity score for each subject:

```
ps <- predict(psmodel, type = "response")
propensity <- cbind(mydata, ps)
```

Plot of propensity score

```
ggplot(propensity, aes(x=ps, fill=as.factor(treatment), group=as.factor(treatment))) +
  geom_histogram(aes(y=-1*..density..) , data = ~ subset(., treatment =="0")) +
  geom_histogram(aes(y=..density..), data = ~ subset(., treatment =="1")) +
  theme_classic() + scale_fill_discrete(name = "Treatment group", labels=c("Control", "RHC")) +
  labs(x="Propensity Score", y="") +
  theme(axis.text.y=element_blank(), axis.ticks.y=element_blank())
```



Step 3: Create weights

Create weights:

```
weight <- ifelse(treatment==1, 1/(ps), 1/(1-ps))
propensity <- propensity %>% mutate(weight=ifelse(treatment==1, 1/ps, 1/(1-ps)))
```

Apply weight to data:

```
weighted_data <- svydesign(ids = ~1, data= mydata, weights = ~weight)
```

Step 4: Check assumptions of IPW

- (Conditional) exchangeablity
- No misspecification of the propensity score model
- Positivity
- Consistency

Step 4: Check assumptions of IPW

Conditional exchangeablity: exposed and unexposed groups are exchangeable

Check the **standardized mean difference** of all known confounders, between exposed and unexposed group after weighting:

```
weighted_table <- svyCreateTableOne(vars = c("age","female", "meanbp1", "apache", "ARF","CHF",
                                             "cirr", "colcan", "coma", "COPD", "lungcan", "MOSF",
                                             "sepsis"), strata = "treatment",
                                    data= weighted_data, test= FALSE, smd= TRUE)
```

```
as.data.frame(print(weighted_table, smd = TRUE))
```

```
##                       Stratified by treatment
##                        0                1                SMD
##    n                    5760.80          5660.88
##    age (mean (SD))       61.37 (17.59)    61.52 (15.22)  0.010
##    female (mean (SD))     0.44 (0.50)      0.44 (0.50)  <0.001
##    meanbp1 (mean (SD))   78.28 (38.20)    78.14 (38.34)  0.004
##    apache (mean (SD))    55.05 (20.43)    55.42 (19.84)  0.018
##    ARF (mean (SD))        0.43 (0.50)      0.45 (0.50)   0.021
##    CHF (mean (SD))        0.08 (0.27)      0.08 (0.27)   0.001
##    cirr (mean (SD))       0.04 (0.19)      0.04 (0.18)   0.017
##    colcan (mean (SD))     0.00 (0.04)      0.00 (0.06)   0.039
##    coma (mean (SD))       0.07 (0.26)      0.07 (0.25)   0.025
##    COPD (mean (SD))       0.08 (0.27)      0.07 (0.26)   0.025
##    lungcan (mean (SD))    0.01 (0.08)      0.01 (0.08)   0.010
##    MOSF (mean (SD))       0.07 (0.25)      0.07 (0.26)   0.008
##    sepsis (mean (SD))     0.22 (0.41)      0.22 (0.41)   0.004
```

Step 4: Check assumptions of IPW

Conditional exchangeablity: exposed and unexposed groups are exchangeable

Compare SMD before and after weighting

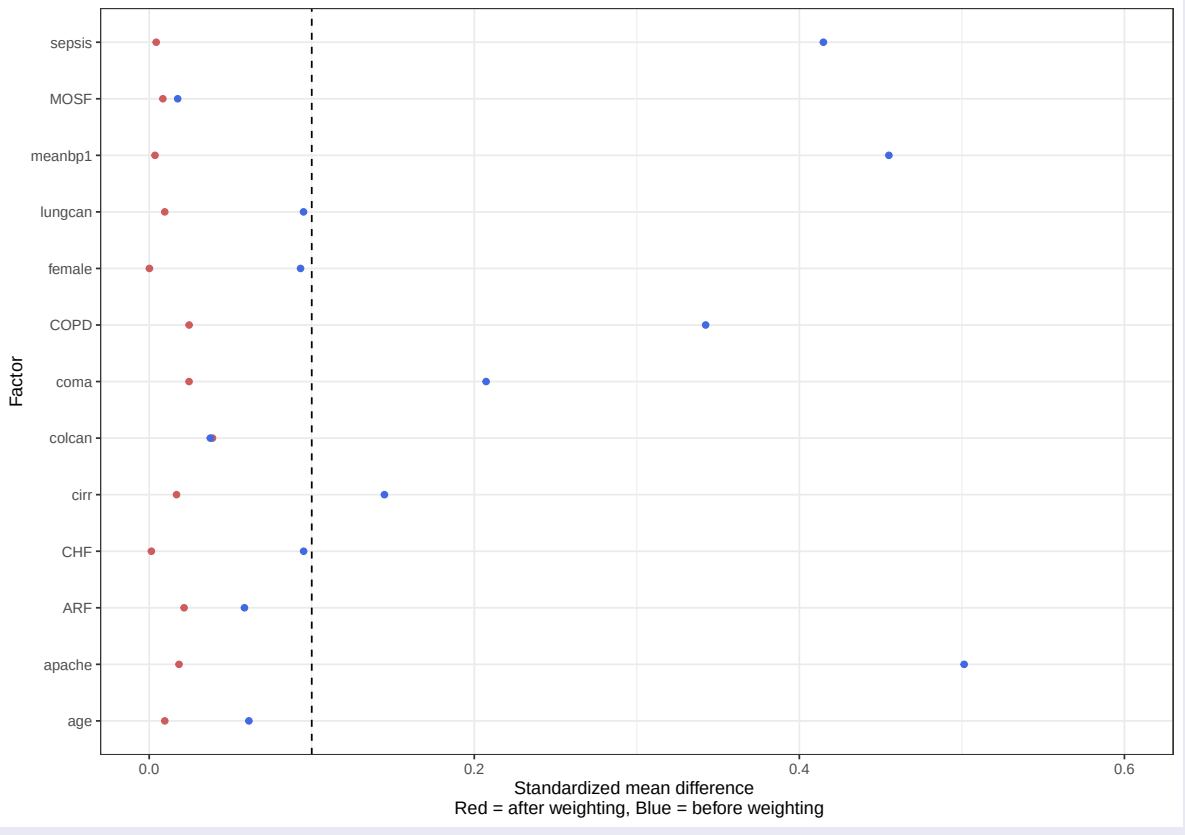
```
raw_data <- svydesign(ids = ~1, data= mydata)
table_raw <- svyCreateTableOne(vars = c("age","female", "meanbp1", "apache", "ARF","CHF",
                                        "cirr", "colcan", "coma", "COPD", "lungcan", "MOSF",
                                        "sepsis"), strata = "treatment",
                               data= raw_data, test= FALSE, smd= TRUE)
```

```
smd <- as.data.frame(cbind(SMD_After= ExtractSmd(weighted_table), SMD_Before = ExtractSmd(table_raw)))
colnames(smd) <- c("SMD_after_weighting", "SMD_before_weighting")
smd$Factor <- rownames(smd)
smd_plot <- ggplot(smd, aes(y = Factor, x =SMD_after_weighting)) +
  geom_point(color="indianred") + xlim(0,0.6) +
  geom_point(aes(y = Factor, x =SMD_before_weighting), color="royalblue") + theme_bw() +
  labs(x="Standardized mean difference \n Red = after weighting, Blue = before weighting") +
  geom_vline(xintercept = 0.1, linetype = "dashed")
```

Step 4: Check assumptions of IPW

Conditional exchangeablity: exposed and unexposed groups are exchangeable

Compare SMD before and after weighting



Calculate the weighted mean manually

Formula (for the treated group):

$$\frac{\sum_{i=1}^{n} I(A_i = 1) * X_i * weight_i}{\sum_{i=1}^{n} I(A_i = 1) * weight_i}$$

- $I(A_i = 1)$: indicator of treatment group of subject i
- X_i : variable to calculate mean
- $weight_i$: weight subject i

Example: calculate weighted mean of age for treated group

```
mean(weight[treatment==1]*age[treatment==1])/(mean(weight[treatment==1]))
```

```
## [1] 61.52427
```

If imbalance after weighting

- Refine propensity score model
  - Interactions between variables?
  - Non-linearity?
- Re-assess balance

Step 4: Check assumptions of IPW

Positivity: there are both exposed and unexposed individuals at each level of every confounder

Check baseline characteristics in original data

	No RHC	RHC
	(N=3551)	(N=2184)
Age		
Mean (SD)	62 (17)	61 (16)
Sex		
Female	1637 (46.1%)	906 (41.5%)
Male	1914 (53.9%)	1278 (58.5%)
APACHE score		
Mean (SD)	51 (19)	61 (20)
Mean blood pressure		
Mean (SD)	85 (39)	68 (34)
Primary disease		
ARF	1581 (44.5%)	909 (41.6%)
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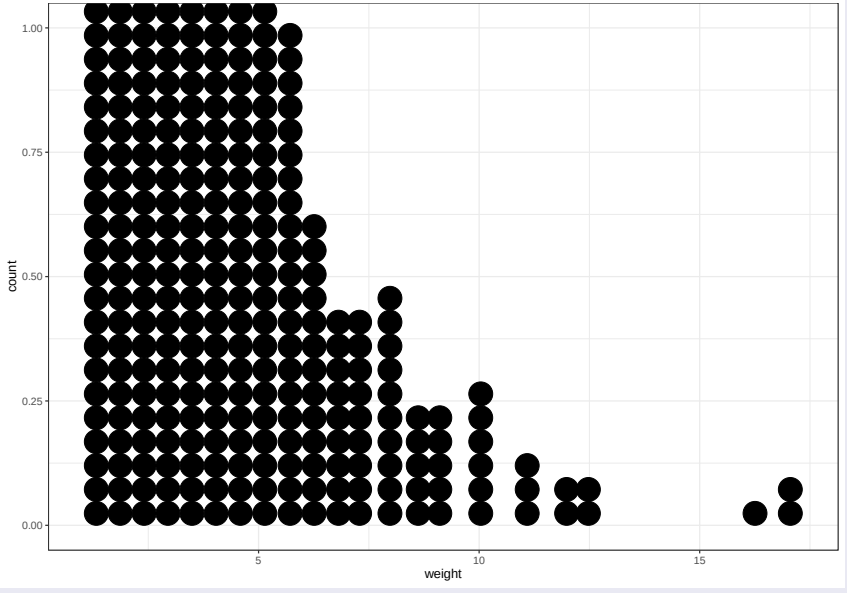
Step 4: Check assumptions of IPW

Positivity: there are both exposed and unexposed individuals at each level of every confounder

Check weight of each individual:

```
ggplot(propensity, aes(weight)) + geom_dotplot() + theme_bw()
```

```
## Bin width defaults to 1/30 of the range of the data. Pick better value with
## `binwidth`.
```



Beware of large weights

!

Large weights lead to noisier estimates of causal effects

- Suppose 1 person has a weight of 1000

$\Rightarrow$ He essentially represents 1000 people

- If the outcome is binary, whether they have the event or not could have a big impact on the parameter estimate

$\Rightarrow$ Standard error estimate(s) will be large

Remedies for large weights

- Investigate why the weights are large
  - Identify individuals with large weights
    - What is unusual about them?
    - Is there a problem with their data?
    - Is there a problem with the propensity score model?

Remedies for large weights

- **Stabilize weights:**

$$sw_i = \frac{P(A_i = a_i)}{P(A_i = a_i | L_i = l_i)}$$

Remedies for large weights

- **Trimming the tails of the propensity socre distribution**
  - i.e. removing subjects with extreme upper and lower values of propensity score
  - Beware: trimming the tails changes the target population
- **Weight truncation**
  - Determine a maximum allowable weight (could be a specific value e.g. 100, or a percentile e.g. 99^{th})
  - If a weight is greater than the maximum allowable, set it to the maximum allowable value
  - Beware: bias-variance trade-off
    - Truncation: bias, but smaller variance
    - No truncation: unbiased, larger variance

Step 4: Check assumptions of IPW

Consistency:

- Design aspect: the exposure/treatment is well defined and any variation within the exposure would not result in a different outcome

Step 5: Fit marginal structural model

Get causal relative risk with weighted GLM:

```
glm_model <- glm(died ~ treatment, weights=weight, family = binomial(link = "log"))
```

```
beta_ipw <- coef(glm_model)
beta_ipw
```

```
## (Intercept)   treatment
## -0.44547711  0.04445993
```

Use asymptotic sandwich variance to properly account for weighting

```
SE <- sqrt(diag(vcovHC(glm_model, type = "HC0")))
```

Get point estimate and 95% CI for Relative Risk:

```
as.data.frame(cbind(causal_RR = exp(beta_ipw[2]),
                    lower_CI = exp(beta_ipw[2] - 1.96*SE[2]),
                    upper_CI = exp(beta_ipw[2] + 1.96*SE[2])))
```

	causal_RR	lower_CI	upper_CI
treatment	1.045463	1.00173	1.091105

Step 5: Fit marginal structural model

Get causal risk difference:

```
glm_model2 <- glm(died ~ treatment, weights=weight, family = binomial(link = "identity"))
beta_ipw2 <- coef(glm_model2)
SE2 <- sqrt(diag(vcovHC(glm_model2, type = "HC0")))
```

```
as.data.frame(cbind(causal_RD = beta_ipw2[2],
                    lower_CI = beta_ipw2[2] - 1.96*SE2[2],
                    upper_CI = beta_ipw2[2] + 1.96*SE2[2]))
```

	causal_RD	lower_CI	upper_CI
treatment	0.0291199	0.0009495	0.0572904

Shortcut: Using IPW package

Calculate weight for each individual:

```
weight_model <- ipwpoint(exposure = treatment, family = "binomial", link = "logit",
                         denominator = ~ age + female + meanbp1 + apache + ARF + CHF + cirr +
                           colcan + coma  + lungcan + MOSF + sepsis, data=mydata)
```

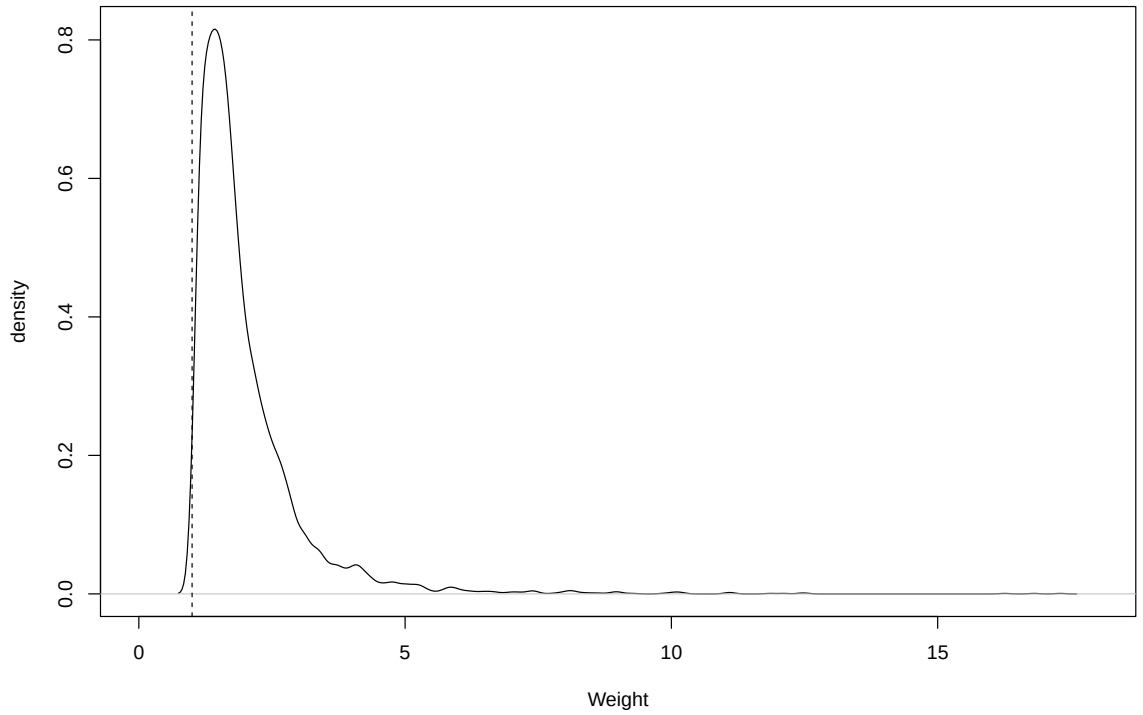
```
summary(weight_model$ipw.weights)
```

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
1.050573	1.374145	1.681879	1.991575	2.238137	17.30117

Shortcut: Using IPW package

Plot weights:

```
ipwplot(weights = weight_model$ipw.weights, logscale = FALSE, xlim=c(0,18), xlab="Weight")
```



Shortcut: Fit MSM using svyglm command

- Advantage: give the right sandwich estimators

```
mydata$wt <- weight_model$ipw.weights
```

- MSM for risk difference

```
msm <- svyglm(died ~ treatment, design = svydesign(~ 1, weight = ~wt, data = mydata))
```

```
coef(msm)
```

```
## (Intercept)   treatment
##  0.64051861  0.02911995
```

```
confint(msm)
```

	2.5 %	97.5 %
(Intercept)	0.6240480	0.6569892
treatment	0.0009417	0.0572982

IPW with truncated weights

Truncates at 1^{st} and 99^{th} percentiles:

```
weight_model_trunc <- ipwpoint(exposure = treatment, family = "binomial", link = "logit",
                         denominator = ~ age + female + meanbp1 + apache + ARF + CHF + cirr +
                           colcan + coma  + lungcan + MOSF + sepsis, data=mydata, trunc = 0.01)
```

```
mydata$wt2 <- weight_model_trunc$ipw.weights
msm2 <- svyglm(died ~ treatment, design = svydesign(~ 1, weight = ~wt2, data = mydata))
coef(msm2)
```

```
## (Intercept)   treatment
##  0.64051861  0.02911995
```

```
confint(msm2)
```

	2.5 %	97.5 %
(Intercept)	0.6240480	0.6569892
treatment	0.0009417	0.0572982

Strengths and Limitations of IPW

Strengths

- Provide estimate on average treatment effect on the whole population
  - While multivariable regression estimates **conditional effects** within the strata of observed covariates
- Summarize all patient characteristics (could be high-dimensional) to a single covariate (the propensity score)
  - While include a large amount of covariates in multivariable regression with few outcomes could cause problems of over-fitting and lack of model convergence.
- Ability to appropriately correct for **time-dependent confounders** in the setting of treatment-confounder feedback
  - While including time-dependent confounders in multivariable regression could cause bias

Strengths and Limitations of IPW

Limitations

- Only valid under assumptions of no unmeasured confounding
  - If unmeasured confouding is present, other methods e.g. instrumental variable or difference-in-difference is needed
- Only perform well under positivity and sufficient overlap of propensity scores between groups

Part 2: IPW for time-dependent confounders and informative censoring

Example: effect of anti-retroviral therapy (ART) on mortality

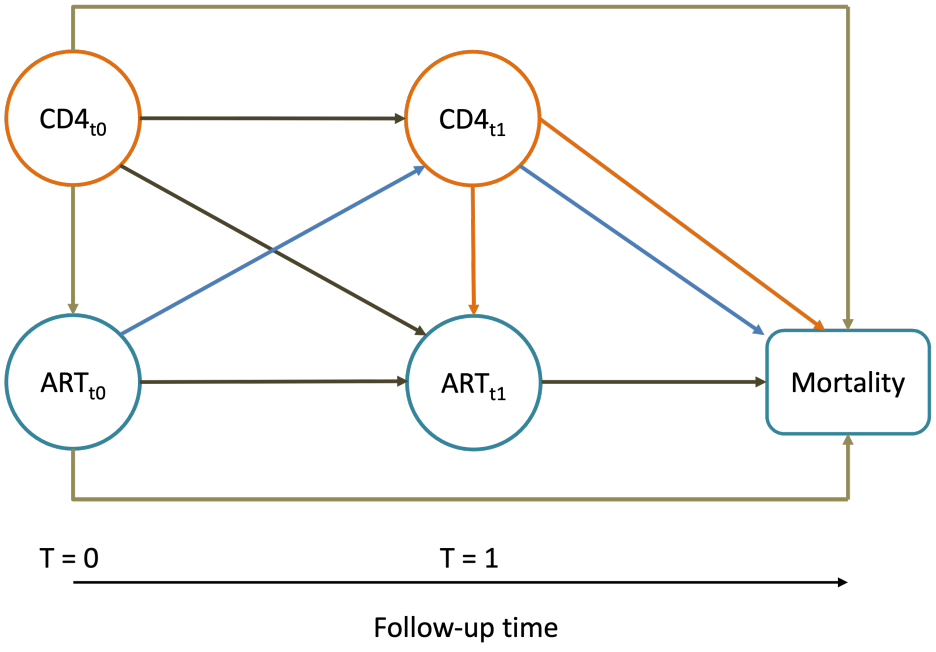
`haartdat` dataset:

```
data("haartdat")
```

- `patient`: patient ID
- `tstart`: starting time for each interval of follow-up, measured is days since HIV seroconversion
- `fuptime`: ending time for each interval of follow-up
- `haartind`: indicator for initiation of ART at the end of each interval. (0 = ART not initiated, 1 = ART initiated)
- `event`: indicator for death at the end of the interval (0 = alive, 1 = died)
- `sex`: 0 = male, 1 = female
- `age`: age of start of follow-up (years)
- `cd4.sqrt`: the square root of CD4 count, measured at the end of each interval, but before `haartind`. Note that in each row, corresponding to time point j in individual i, `cd4.sqrt` has an effect on `haartind` in the same row, including at time 0
- `dropout`: indicator for dropout of the study, at the end of the interval (0 = did not drop out, 1 = dropped out).

Time-dependent confounders

Time-dependent confounders



- $CD4_{t1}$ is a confounder of ART_{t1} and outcome Mortality (pathway in red)
- $CD4_{t1}$ is also a mediator of ART_{t0} and outcome Mortality (pathway in blue)

$\Rightarrow$ Adjusting for time-dependent confounder $CD4_{t1}$ may inappropriately block the effect of past exposure ART_{t0} on outcome Mortality

Remedy: IPW for time-dependent confounder

- Separate weight is calculated for each measurement at each time point individually
- This creates a pseudo-population in which covariate balance between groups is achieved over time and ensures that the exposure status is no longer affected by previous exposure nor confounders

Applying on `haartdat` data

Step 1 Calculate weights

- For a given individual i, the weight up to time point j is calculated as the product over all time points from baseline up to time point j of the inverse of the probability of the exposure status at each time point (a_{ik}), given
  - the **exposure history** up to the previous time point $(\overline{a}_{ik-1})$
  - the observed history of **time-varying confounder**$(\overline{c}_{ik})$
  - the observed time-fixed covariates (v_i)

$$w_{ij} = \prod_{k=0}^{j} \frac{1}{P(A_{ik} = a_{ik} | \overline{A}_{ik-1} = a_{ik}, \overline{C}_{ik} = \overline{c}_{ik}, V_i = v_i)}$$

Applying on `haartdat` data

- Alternatively, we could use stabilized weights:

$$w_{ij} = \prod_{k=0}^{j} \frac{P(A_{ik} = a_{ik} | \overline{A}_{ik-1} = a_{ik}, V_i = v_i)}{P(A_{ik} = a_{ik} | \overline{A}_{ik-1} = a_{ik}, \overline{C}_{ik} = \overline{c}_{ik}, V_i = v_i)}$$

In the `haarttdat`:

- Time-varying exposure A_{ik}: ART treatment
- Time-varying confounder $\overline{C}_{ik}$: CD4 count
- Time-fixed covariates: V_i sex and age

Applying on `haartdat` data

- Stabilized weight:

$$w_{ij} = \prod_{k=0}^{j} \frac{P(A_{ik} = a_{ik} | \overline{A}_{ik-1} = a_{ik}, V_i = v_i)}{P(A_{ik} = a_{ik} | \overline{A}_{ik-1} = a_{ik}, \overline{C}_{ik} = \overline{c}_{ik}, V_i = v_i)}$$

- Estimate the elements in the denominator by Cox proportional hazards model

$$\lambda_{ART}[t|CD4(t), V, ART(t)] = \lambda_0(t) exp(\beta_1 * CD4(t) + \beta_2' V)$$

- Estimate the elements in the numerator by similar Cox proportional hazards model but without $CD4(t)$ as predictor

Applying on `haartdat` data

- Calculate weights

```
temp <- ipwtm(exposure = haartind, family = "survival", numerator = ~ sex + age,
              denominator = ~cd4.sqrt + sex + age, id = patient, tstart = tstart,
              timevar = fuptime, type = "first", data = haartdat)
summary(temp$ipw.weights)
```

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.2458796	0.9035718	0.9861653	1.03896	1.061069	7.125717

- Compare with unstabilized weights:

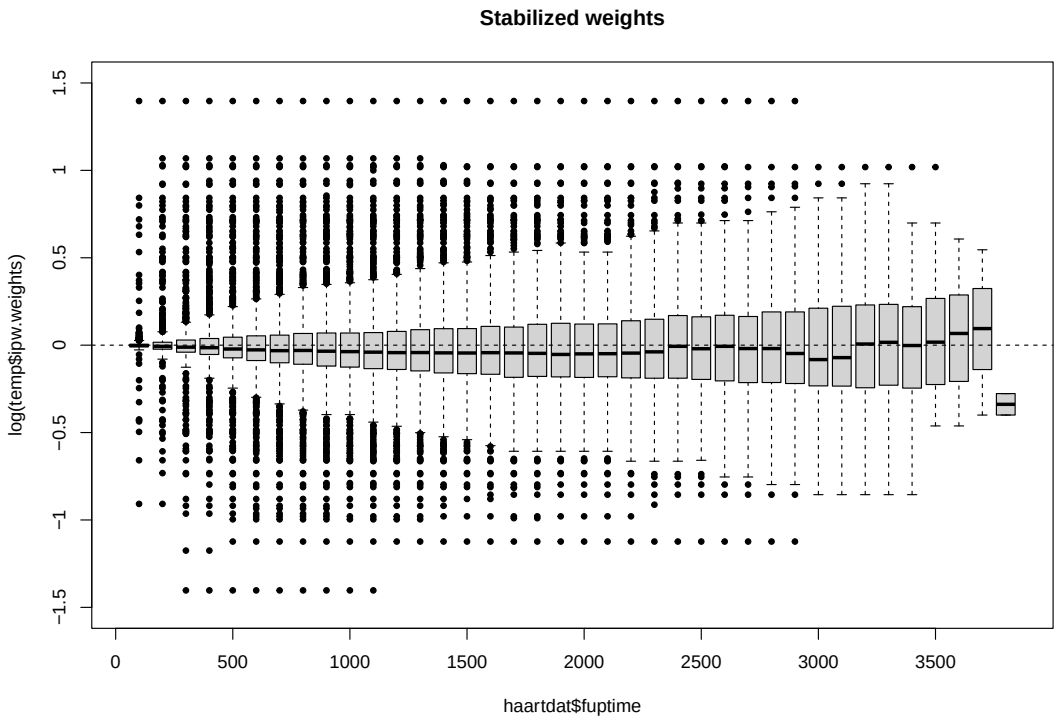
```
temp.unstab <- ipwtm(exposure = haartind, family = "survival",
              denominator = ~cd4.sqrt + sex + age, id = patient, tstart = tstart,
              timevar = fuptime, type = "first", data = haartdat)
summary(temp.unstab$ipw.weights)
```

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
1.002791	1.160204	1.37223	13.16067	15.40092	406.338

Applying on haartdat data

Step 2: investigating weights

```
ipwplot(weights = temp$ipw.weights, timevar = haartdat$fuptime, binwidth = 100, ylim = c(-1.5, 1.5),
        main="Stabilized weights", xaxt="n", yaxt="n")
axis(side = 1, at = c(0, 5, 10, 15, 20, 25, 30, 35),
     labels = as.character(c(0, 5, 10, 15, 20, 25, 30, 35)*100))
axis(side = 2, at = c(-1.5, -1, -0.5, 0, 0.5, 1, 1.5),
     labels = as.character(c(-1.5, -1, -0.5, 0, 0.5, 1, 1.5)))
```



Applying on `haartdat` data

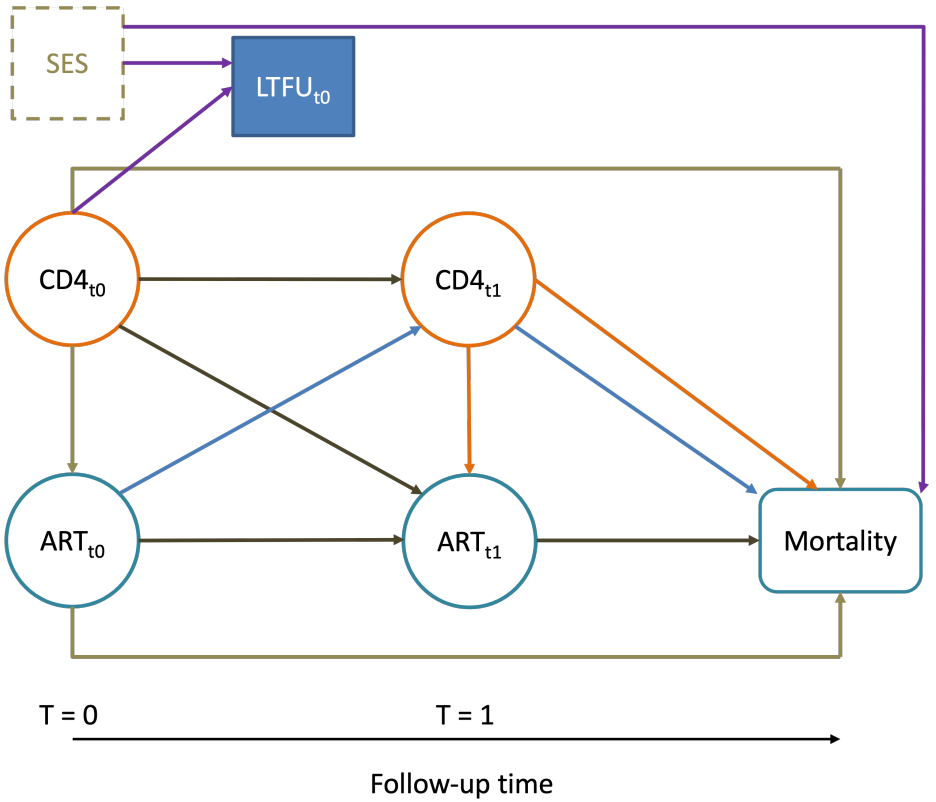
Step 3: Fit the marginal structural model

Using robust variance estimator (through `cluster()`)

```
mort_model <- coxph(Surv(tstart, fuptime, event) ~ haartind + cluster(patient),
                    data = haartdat, weights = temp$ipw.weights)
summary(mort_model)
```

```
## Call:
## coxph(formula = Surv(tstart, fuptime, event) ~ haartind, data = haartdat,
##     weights = temp$ipw.weights, cluster = patient)
##
##   n= 19175, number of events= 31
##
##             coef exp(coef) se(coef) robust se      z Pr(>|z|)
## haartind -0.9921    0.3708   0.4491    0.4613 -2.151   0.0315 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## haartind    0.3708      2.697    0.1501    0.9158
##
## Concordance= 0.597  (se = 0.03 )
## Likelihood ratio test= 5.81  on 1 df,   p=0.02
## Wald test            = 4.62  on 1 df,   p=0.03
## Score (logrank) test = 5.26  on 1 df,   p=0.02,   Robust = 5.43  p=0.02
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

Informative censoring



- Individuals with low SES are more likely to be lost-to-follow-up, and also more likely to die

$\Rightarrow$ Informative censoring: fewer deaths in those remaining, underestimate mortality

Remedy: IPW for informative censoring

- Account for informative censoring by upweighting those remaining in the study, who have similar characteristics to those who were censored
- The inverse probability of censoring weights (IPCWs) are calculated for each time point as the inverse probability of remaining in the study up to the current time point, given the previous exposure, and patient characteristics related to censoring.
- To obtain the overall weight of each individual: multiply IPCW with the inverse probability of treatment weights

Applying on `haartdat` data

- Estimate IPCWs

```
temp2 <- ipwtm(exposure = dropout, family = "survival", numerator = ~ sex + age,
               denominator = ~cd4.sqrt + sex + age, id = patient, tstart = tstart,
               timevar = fuptime, type = "first", data = haartdat)
summary(temp2$ipw.weights)
```

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
0.5640002	0.9874624	0.9998046	0.9985541	1.010292	2.334772

Applying on haartdat data

- Fit the MSM model

```
mort_model2 <- coxph(Surv(tstart, fuptime, event) ~ haartind + cluster(patient),
                     data = haartdat, weights = temp$ipw.weights*temp2$ipw.weights)
summary(mort_model2)
```

```
## Call:
## coxph(formula = Surv(tstart, fuptime, event) ~ haartind, data = haartdat,
##     weights = temp$ipw.weights * temp2$ipw.weights, cluster = patient)
##
##   n= 19175, number of events= 31
##
##             coef exp(coef) se(coef) robust se      z Pr(>|z|)
## haartind -0.9378    0.3915   0.4300    0.4524 -2.073   0.0382 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## haartind    0.3915      2.554    0.1613    0.9501
##
## Concordance= 0.597  (se = 0.029 )
## Likelihood ratio test= 5.59  on 1 df,   p=0.02
## Wald test            = 4.3  on 1 df,   p=0.04
## Score (logrank) test = 5.08  on 1 df,   p=0.02,   Robust = 4.85  p=0.03
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

Applying on `haartdat` data

- Comparing with time-varying Cox model without IPW:

```
mort_model3 <- coxph(Surv(tstart, fuptime, event) ~ haartind +
                       cluster(patient) + cd4.sqrt + sex + age, data = haartdat)
summary(mort_model3)
```

```
## Call:
## coxph(formula = Surv(tstart, fuptime, event) ~ haartind + cd4.sqrt +
##     sex + age, data = haartdat, cluster = patient)
##
##   n= 19175, number of events= 31
##
##              coef exp(coef) se(coef) robust se      z Pr(>|z|)
## haartind -0.61994   0.53798  0.43837   0.41971 -1.477 0.139657
## cd4.sqrt -0.13125   0.87700  0.03440   0.04682 -2.803 0.005060 **
## sex       0.04408   1.04507  0.47194   0.45187  0.098 0.922282
## age       0.05943   1.06123  0.01522   0.01657  3.588 0.000334 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##          exp(coef) exp(-coef) lower .95 upper .95
## haartind     0.538     1.8588    0.2363    1.2247
## cd4.sqrt     0.877     1.1403    0.8001    0.9613
## sex          1.045     0.9569    0.4310    2.5338
## age          1.061     0.9423    1.0273    1.0963
##
## Concordance= 0.708  (se = 0.056 )
## Likelihood ratio test= 31.53  on 4 df,   p=2e-06
## Wald test            = 25.36  on 4 df,   p=4e-05
## Score (logrank) test = 33.72  on 4 df,   p=8e-07,   Robust = 12.13  p=0.02
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

Conclusions

- IPW is a robust method to estimate unbiased causal effect of exposure on outcome, particularly in the setting of time-dependent confounding and informative censoring
- However IPW only works under strict assumptions
- Need to carefully assess assumptions and balance after weighting to ensure validity of results
- Advisable: perform sensitivity analysis of different causal inference methods


THANK YOU
FOR YOUR
ATTENTION

References

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- van der Wal WM, Geskus RB. ipw: An R Package for Inverse Probability Weighting. Journal of Statistical Software. 2011;43(13):1 - 23.
- Shiba K, Kawahara T. Using Propensity Scores for Causal Inference: Pitfalls and Tips. J Epidemiol. 2021;31(8):457-63.