Practical 2

Part 1 or 3: Assumptions in causal inference

(a) We investigate the effect of a specific motivational training on the performance of students in elementary school. We recruit several school classes and in each class, we randomly allocate one half of the students to the motivational training, while the other half serves as the control group.

(i) It is likely that the students in the motivation group share what they learned in the motivational training with the other students. Which assumption is violated? *'no interference'*

(ii) Name sources of (unobserved) confounding in this study, if any. *Since the study is randomised, there is no confounding.*

Additional note: Confounding threatens internal validity. While confounding is not an issue in this study, in practice external validity would need to be discussed, e.g. whether the school classes are representative for the target population.

(b) We are interested in the effect of antihypertensives (drugs that lower the blood pressure) on the incidence of chronic heart disease (CHD). Our data base contains information on prescribed antihypertensives, CHD and further health-related as well as demographic information for a large number of patients over time.

(i) There are several different classes of antihypertensives that lower the blood pressure by different means. Some of them are never prescribed to patients with specific comorbidities (e.g. diuretics are contra-indicated in patients suffering from chronic obstructive pulmonary disease). Which assumption(s) may be violated? How could the research question be modified? *The consistency assumption may be violated: without further subject-matter arguments, we must assume that the potential outcome of a given patient treated with antihypertensive A is different from the potential outome of the same patient treated with antihypertensive B. Further, positivity is violated because not all treatments are possible for all possible covariate values. As for an alternative research question, we could e.g. restrict ourselves to one specific drug.*

(ii) Name sources of (unobserved) confounding in this study, if any. *Observed confounders would (probably) include age, sex, BMI, comorbidities, reported smoking status and medical history. Unobserved might be 'lifestyle' (including more precise smoking and dietary information) or underlying healthiness.*

Part 3: Adjustment using standardisation and IPTW by hand

The following examples are taken from the book *Causal Inference: What If*, by Miguel Hernán and Jamie Robins.

	$Y(0)$	$Y(1)$
Rheia	0	1
Kronos	1	0
Demeter	0	0
Hades	0	0
Hestia	0	0
Poseidon	1	0
Hera	0	0
Zeus	0	1
Artemis	1	1
Apollo	1	0
Leto	0	1
Ares	1	1
Athena	1	1
Hephaestus	0	1
Aphrodite	0	1
Cyclope	0	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0
Σ	10	10

	X	C	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	1	0	0
Poseidon	1	0	0
Hera	1	0	0
Zeus	1	0	1
Artemis	0	1	1
Apollo	0	1	1
Leto	0	1	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Cyclope	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0
Σ	13	12	10

(a) The **right**-hand table contains data for twenty Greek gods waiting for heart transplants. The variable X describes the treatment ($X = 0$ no transplant received, $X = 1$ transplant received). The outcome of interest is survival five years after treatment ($Y = 0$ alive, $Y = 1$ dead). By divine revelation we know the potential outcomes for each of the gods, shown in the left-hand table.

(i) Is there an individual causal effect for Zeus? *yes, because* $Y(0) \neq Y(1)$

(ii) What is the average causal effect? (causal risk difference)

$$\mathsf{ACE} = P(Y(1) = 1) - P(Y(0) = 1) = 10/20 - 10/20 = 0$$

(b) The **right**-hand table contains related data from an observational study. Shown are the actual treament X, the actual outcome Y and a risk factor C. Assume that within strata of C, the treatment X can be considered like randomised. Fill in the missing numbers in the following (the gaps are labelled for easier reference).

(i) The crude (unadjusted) difference is
$\Delta = \hat{P}(Y = 1 \mid X = 1) - \hat{P}(Y = 1 \mid X = 0) = 7/13 - 3/7 \approx 0.1$ (1).

This (wrongly!) suggests that treatment increases the risk of death by 10 %.

(Compare this to the average causal effect from a)(ii) – association is not causation!)

(ii) Estimate the average causal effect via standardisation (see slide 46).
Subgroup with $C = 0$:
The estimated risk of dying when treated is
$\hat{P}(Y = 1 \mid X = 1, C = 0) = 1/4$ (2).
The estimated risk of dying when untreated is
$\hat{P}(Y = 1 \mid X = 0, C = 0) = 1/4$ (3).

Subgroup with $C = 1$:
The estimated risk of dying when treated is
$\hat{P}(Y = 1 \mid X = 1, C = 1) = 2/3$ (4).
The estimated risk of dying when untreated is
$\hat{P}(Y = 1 \mid X = 0, C = 1) = 2/3$ (5).

Standardisation:
The estimated standardised risk of dying for the whole population when treated is
$\hat{P}(Y(1) = 1)$
$= \hat{P}(Y = 1 \mid X = 1, C = 0) \cdot \hat{P}(C = 0) + \hat{P}(Y = 1 \mid X = 1, C = 1) \cdot \hat{P}(C = 1)$
$= 1/4 \cdot 8/20 + 2/3 \cdot 12/20 = 0.5$ (6).
The estimated standardised risk of dying for the whole population when untreated is
$\hat{P}(Y(0) = 1)$
$= \hat{P}(Y = 1 \mid X = 0, C = 0) \cdot \hat{P}(C = 0) + \hat{P}(Y = 1 \mid X = 0, C = 1) \cdot \hat{P}(C = 1)$
$= 1/4 \cdot 8/20 + 2/3 \cdot 12/20 = 0.5$.
The estimated average causal effect is
$\hat{ACE} = \hat{P}(Y(1) = 1) - \hat{P}(Y(0) = 1) = 0.5 - 0.5 = 0$ (8).
(Compare this to the average causal effect from a)(ii).)

(iii) Estimate the average causal effect via inverse probability of treatment weighting (see slide 57ff.).
The estimated probability of treatment given $C = 0$ is
$\hat{P}(X = 1 \mid C = 0) = 1/2$ (9).
The estimated probability for having $C = 0$, being treated and dying is
$\hat{P}(C = 0, X = 1, Y = 1) = 1/20$ (10).
Weighting with the inverse probability of treatment given $C = 0$ yields
$\frac{\hat{P}(C=0,X=1,Y=1)}{\hat{P}(X=1|C=0)} = 1/10$ (11).
The estimated probability for having $C = 0$, not being treated and dying is
$\hat{P}(C = 0, X = 0, Y = 1) = 1/20$ (12).
Weighting with the inverse probability of no treatment given $C = 0$ yields
$\frac{\hat{P}(C=0,X=0,Y=1)}{\hat{P}(X=0|C=0)} = 1/10$ (13).

The estimated probability of treatment given $C = 1$ is
$\hat{P}(X = 1 \mid C = 1) = 3/4$ (14).
The estimated probability for having $C = 1$, being treated and dying is
$\hat{P}(C = 1, X = 1, Y = 1) = 6/20$ (15).

Weighting with the inverse probability of treatment given $C = 0$ yields $\frac{\hat{P}(C=1,X=1,Y=1)}{\hat{P}(X=1|C=1)} = 4/10$ (16).
The estimated probability for having $C = 1$, not being treated and dying is $\hat{P}(C = 1, X = 0, Y = 1) = 1/10$ (17).
Weighting with the inverse probability of no treatment given $C = 1$ yields $\frac{\hat{P}(C=1,X=0,Y=1)}{\hat{P}(X=0|C=1)} = 4/10$ (18).

The estimated weighted risk of dying for the whole population when treated is $\hat{P}(Y(1) = 1) = \frac{\hat{P}(C=0,X=1,Y=1)}{\hat{P}(X=1|C=0)} + \frac{\hat{P}(C=1,X=1,Y=1)}{\hat{P}(X=1|C=1)} = 0.5$ (19).
The estimated weighted risk of dying for the whole population when not treated is
$\hat{P}(Y(0) = 1) = \frac{\hat{P}(C=0,X=0,Y=1)}{\hat{P}(X=0|C=0)} + \frac{\hat{P}(C=1,X=0,Y=1)}{\hat{P}(X=0|C=1)} = 0.5$ (20).
The estimated average causal effect is
$\hat{ACE} = \hat{P}(Y(1) = 1) - \hat{P}(Y(0) = 1) = 0.5 - 0.5 = 0$ (21).
(Compare this to the average causal effect from a)(ii).)

Part 3: (Augmented) IPTW

(a) Consider an exposure A (binary), a sufficient set of covariates X (discrete), and an outcome Y; assume $\pi(x) = P(A = 1|X = x)$ is known.
Show that $\mathbb{E}[AY/\pi(X)] = \mathbb{E}[Y|\text{do}(A = 1)]$ or $\mathbb{E}[AY/\pi(X)] = \mathbb{E}Y(1)$. State clearly on what assumptions you rely. (Trick: use iterated conditional expectation.)

Positivity ensures that division by $\pi(X)$ is well-defined. We rewrite $\mathbb{E}[AY/\pi(X)]$ using conditional iterated expectation and exploit the fact that A is binary:

$$\begin{aligned}\mathbb{E}\frac{AY}{\pi(X)} &= \mathbb{E}_X\mathbb{E}_A\left[\mathbb{E}_Y\left[\frac{AY}{\pi(X)}\middle| A, X\right]\middle| X\right] \\ &= \mathbb{E}_X\left\{\mathbb{E}_Y\left[\frac{Y}{\pi(X)}\middle| A = 1, X\right] P(A = 1 \mid X)\right\} \\ &= \mathbb{E}_X\mathbb{E}_Y[Y \mid A = 1, X]\,.\end{aligned}$$

The last equality follows because given $X = x$, $\pi(x)$ is a constant and cancels out with $P(A = 1 \mid X = x)$. We can now proceed using either the do-operator or potential outcomes. Using do, no unobserved confounding given X implies that

$$\mathbb{E}_X\mathbb{E}_Y[Y \mid A = 1, X] = \mathbb{E}_X\mathbb{E}_Y[Y \mid do(A = 1), X] = \mathbb{E}[Y \mid do(A = 1)].$$

Using potential outcomes, it follows by consistency and no unobserved confounding that

$$\mathbb{E}_X\mathbb{E}_Y[Y \mid A = 1, X] = \mathbb{E}_X\mathbb{E}[Y(1) \mid A = 1, X] = \mathbb{E}_X\mathbb{E}[Y(1) \mid X] = \mathbb{E}Y(1).$$

Note that no-interference comes in when we use a sample of N units, replacing expectations by sample averages, and assume that the units are each only affected by their own treatment.

(b) In the same situation as above:

(i) show that for

$$\hat{\mu}_1 = m(X) + \frac{A}{\pi(X)}(Y - m(X))$$

we have: $\mathbb{E}\hat{\mu}_1 = \mathbb{E}[Y|\text{do}(A = 1)]$ if either $m(X) = \mathbb{E}[Y \mid A = 1, X]$ or if $\pi(x) = P(A = 1|X = x)$.

scenario 1: $m(X) = \mathbb{E}[Y \mid A = 1, X]$

$$\begin{aligned}\mathbb{E}\hat{\mu}_1 &= \mathbb{E}_X\left\{\mathbb{E}[Y \mid A = 1, X] + \frac{A}{\pi(X)}(Y - \mathbb{E}[Y \mid A = 1, X])\right\} \\ &= \mathbb{E}_X\mathbb{E}[Y \mid A = 1, X] + \underbrace{\mathbb{E}\frac{A}{\pi(X)}(Y - \mathbb{E}[Y \mid A = 1, X])}_{\substack{=\mathbb{E}_X\mathbb{E}_A\left(\mathbb{E}_Y\left(\frac{A}{\pi(X)}(Y-\mathbb{E}(Y|A=1,X))|A,X\right)|X\right) \\ =\mathbb{E}_X\left\{\frac{1}{\pi(X)}\mathbb{E}_Y[Y-\mathbb{E}[Y|A=1,X]|\,A=1,X]P(A=1|X)\right\}=0}} \\ &= \mathbb{E}_X\mathbb{E}[Y(1) \mid A = 1, X] \\ &= \mathbb{E}Y(1)\end{aligned}$$

scenario 2: $\pi(x) = P(A = 1 \mid X = x)$. *Convince yourself that* $\hat{\mu}_1$ *can be re-written as in the slides.*

$$\begin{aligned}
\mathbb{E}\hat{\mu}_1 &= \mathbb{E}\left\{ \frac{A}{P(A=1 \mid X)} Y + \left(1 - \frac{A}{P(A=1 \mid X)}\right) m(X) \right\} \\
&= \mathbb{E}\frac{AY}{P(A=1 \mid X)} + \mathbb{E}_X \Bigg\{ \underbrace{\mathbb{E}_A \left[\left(1 - \frac{A}{P(A=1 \mid X)}\right) m(X) \,\middle|\, X \right]}_{=0} \Bigg\} \\
&= \mathbb{E}Y(1),
\end{aligned}$$

where the last line is as for the IPTW estimator.

(ii) What does the corresponding $\hat{\mu}_0$ have to look like?

$$\hat{\mu}_0 = m(X) + \frac{1 - A}{1 - \pi(X)} (Y - m(X))$$

Note that this has expectation $\mathbb{E}Y(0)$ *if* $\pi(X)$ *is the correct propensity score or if* $m(X) = \mathbb{E}[Y \mid A = 0, X]$.

Part 3: Causal effect estimation with R

You can find instructions to install all required packages and data sets here:

`https://github.com/bips-hb/APTS_Causal_Inference`

Solutions will be placed on the above GitHub space in an R markdown format.

Consider the 'Rotterdam breastcancer' data on 2982 women diagnosed with primary breast cancer – this is in the file `bcrot`. This was an observational study and interest lies in estimating the average causal effect of hormonal therapy (`hormon` binary yes/no) on a synthetic outcome `qol` (health related quality of life, continuous measure). The following covariates are included: `age` = age at diagnosis; `nodes` = number of positive lymph nodes (exp-transformed to `enodes`); `pr_1` = Progestorone receptors (fmol/l) (log-transformed).

(a) Compare descriptively QOL for those who do and do not take hormonal therapy.

(b) Carry out some descriptive analyses (including overlap plots using a flexible model for the propensity score) to investigate the positivity assumption. Convince yourself that it makes sense to restrict the sample to those $\geq$40 years and with at least one node. Create a dataset containing this restricted sample.

(c) Use IPTW to estimate the average causal effect in the restricted population (either 'by hand' or with `R` package `ipw`); investigate extreme weights and consider covariate balance of the re-weighted sample (`R` package `cobalt`, function `love.plot`).

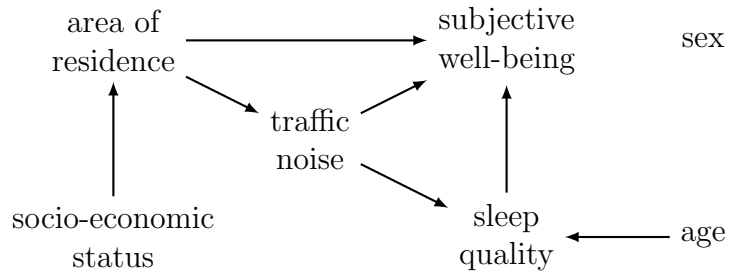
(d) Use regression standardisation to estimate the average causal effect in the restricted population (`R` package `stdReg`) choosing a flexible outcome model.

(e) Finally, use `AIPTW` to estimate the average causal effect in the restricted population (R package `AIPW` with default settings and super-learner). Investigate the covariance balance for the re-weighted sample.

(f) Compare all the above estimates including their precision (ensure that you take the behaviour of the IPT-weights into account).

Note that the covariates are from a real dataset, but the quality of life outcome in the above data is fictitious!

Part 4: Causal DAGs and regression



The figure above shows a fictional causal DAG.

(a) Which statements are correct, given the causal DAG above? *Note that here we assume that the DAG has been elicited based on expert knowledge; it was not found by causal discovery methods; hence we assume the Markov properties (every separation entails a conditional independence) but not necessarily faithfulness.*

(i) In a regression of 'subjective well-being' on 'age' and 'sex', we expect both coefficients to be zero. *We expect the coefficient of 'sex' to be zero. We expect the coefficient of 'age' to be either zero or non-zero depending on whether the regression model is correctly specified and on the strength of the association. In a correctly specified model, this coefficient would describe the total effect on the chosen scale.*

(ii) The coefficients in a regression of 'sleep quality' on 'traffic noise', 'subjective well-being' and 'age' have a causal interpretation. *No, as we regress on an effect of sleep quality, the coefficients in this regression do not have a causal interpretation.*

(iii) The coefficients in a regression of 'subjective well-being' on 'traffic noise' and 'sleep quality' have a causal interpretation. *This is an example of the 'table 2 fallacy': The coefficient of 'sleep quality' has a causal interpretation as a conditional effect (given traffic noise level (in a correct model)), but the effect of traffic noise is confounded by 'area of residence'. Displaying both coefficients in the same table may lead to confusion.*

(iv) If we regress 'sleep quality' on 'age' and obtain a coefficient of about zero, we know that the DAG is wrong. *No. Assuming only the Markov properties, an edge in a DAG is compatible with a zero effect (while a missing edge always implies a zero effect). Under faithfulness this is excluded.*

(b) Suppose we are interested in the total causal effect of 'sleep quality' on 'subjective well-being.' Which confounders should we adjust for? How could the desired effect be obtained? *We need to adjust for 'traffic noise' and may additionally adjust for 'area of residence' in order to increase the efficiency, depending on the method we use for adjustment. For example, we could regress 'subjective well-being' on 'sleep quality' and 'traffic noise' and standardise over 'traffic noise'. Alternatives to regression adjustment are e.g. inverse probability of treatment weighting and propensity score matching. In this specific (rather unrealistic) example, we could even follow an instrumental variable approach with 'age' as an instrument.*