Causal Inference

a summary

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1 General

Causal Roadmap (Petersen and van der Laan, 2014) systematic approach linking causality to statistical procedures

1. Specifying Knowledge. structural causal model (unifying counterfactual language, structural equations, & causal graphs): a set of possible data-generating processes, expresses background knowledge and its limits

2. Linking Data. specifying measured variables and sampling specifics (latter can be incorporated into the model)

3. Specifying Target. define hypothetical experiment: decide

1. variables to intervene on: one (point treatment), multiple (longitudinal, censoring/missing, (in)direct effects)
2. intervention scheme: static, dynamic, stochastic
3. counterfactual summary of interest: absolute or relative, marginal structural models, interaction, effect modification
4. population of interest: whole, subset, different population

4. Assessing Identifiability. are knowledge and data sufficient to derive estimand and if not, what else is needed?

5. Select Estimand. current best answer: knowledge-based assumptions + which minimal convenience-based asspumptions (transparency) gets as close as possible

6. Estimate. choose estimator by statistical properties, nothing causal here

7. Interpret. hierarchy: statistical, counterfactual, feasible intervention, randomized trial

Average Causal Effect $\mathrm{E}\left[Y^{a=1}\right] \neq \mathrm{E}\left[Y^{a=0}\right]$

$$\mathrm{E}\left[Y^{a}\right] = \sum_{y} y p_{Y^a}(y) \qquad \text{(discrete)}$$

$$= \int y f_{Y^a}(y) dy \qquad \text{(continuous)}$$

individual causal effect $Y_i^{a=1} \neq Y_i^{a=0}$ generally unidentifiable

null hypothesis: no average causal effect

sharp null hypothesis: no causal effect for any individual

notation A, Y: random variables (differ for individuals); a, y: particular values; counterfactual $Y^{a=1}$: Y under treatment $a = 1$

stable unit treatment value assumption (SUTVA) Y_i^a is well-defined: no interference between individuals, no multiple versions of treatment (weaker: treatment variation irrelevance)

causal effect measures typically based on means

risk difference: $\Pr\left[Y^{a=1}=1\right] - \Pr\left[Y^{a=0}=1\right]$

risk ratio: $\frac{\Pr\left[Y^{a=1}=1\right]}{\Pr\left[Y^{a=0}=1\right]}$

odds ratio: $\frac{\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=1}=0\right]}{\Pr\left[Y^{a=0}=1\right]/\Pr\left[Y^{a=0}=0\right]}$

number needed to treat (NNT) to save 1 life: -1/risk difference

sources of random error: sampling variability (use consistent estimators), nondeterministic counterfactuals

association compares $E\left[Y|A=1\right]$ and $E\left[Y|A=0\right]$, **causation** compares $E\left[Y^{a=1}\right]$ and $E\left[Y^{a=0}\right]$ (whole population)

Target Trial emulating an ideal randomized experiment explicitly formulate target trial & show how it is emulated → less vague causal question, helps spot issues

missing data problem unknown counterfactuals

randomized experiments: missing completely at random → exchangeability (= exogeneity as treatment is exogenous)

ideal randomized experiment: no censoring, double-blind, well-defined treatment, & adherence → association is causation

pragmatic trial: no placebo/blindness, realistic monitoring

PICO (population, intervention, comparator, outcome): some components of target trial

three types of causal effects:

intention-to-treat effect (effect of treatment assignment)

per-protocol effect (usually dynamic when toxicity arises)

other intervention effect (strategy changed during follow-up)

controlled direct effects: effect of A on Y not through B

natural direct effect A on Y if $B^{a=0}$ (cross-world quantity)

principal stratum effect A on Y for subset with $B^{a=0} = B^{a=1}$

crossover experiment: sequential treatment & outcome t=0, 1 individual causal effect $Y_{it}^{a_t=1} - Y_{it}^{a_t=0}$ only identifiable if: no carryover effect, effect $\perp\!\!\!\perp$ time, outcome $\perp\!\!\!\perp$ time

time zero if eligibility at multiple t (observational data): earliest, random t, all t (adjust variance with bootstrapping)

grace periods: usually treatment starts x months after first eligible, if death before: randomly assign strategy/copy into both

Identifiability Conditions hold in ideal experiments

consistency counterfactuals correspond to data $Y = Y^A$: if $A = a$, then $Y^a = Y$ for each individual

- precise definition of Y^a via specifying a (sufficiently well-defined a maybe impossible (effect of DNA before it was discovered), relies on expert consensus)
- linkage of counterfactuals to data (a must be seen in data)

positivity $\Pr\left[A = a|L = l\right] > 0 \ \forall\, l$ with $\Pr\left[L = l\right] > 0$;

$$f_L(l) \neq 0 \Rightarrow f_{A|L}(a|l) > 0 \ \forall a, l$$

- structural violations (inference not on full population)
- random variability (smooth over with parametric models)

can sometimes be empirically verified (if all is seen in data)

exchangeability unverifiable without randomization

- *marginal:* $Y^a \perp\!\!\!\perp A \mathrel{\widehat{=}}$ randomized experiment, counterfactuals are missing completely at random (MCAR)
- *conditional:* $Y^a \perp\!\!\!\perp A|L \mathrel{\widehat{=}}$ conditionally randomized, counterfactuals are missing at random (MAR)

alternative definition: $\Pr\left[A = 1|Y^{a=0}, L\right] = \Pr\left[A = 1|L\right]$

additional conditions:

correct measurement mismeasurement of A, Y, L results in bias

correct model specification models $\overset{\text{may}}{\rightarrow}$ misspecification bias

Effect Modification A on Y varies across levels of V

null average causal effect ≠ null causal effect per subgroup

population characteristics: causal effect measure is actually "effect in a population with a particular mix of effect modifiers"

transportability: extrapolation of effect to another population (issues: effect modification, versions of treatment, interference)

effects conditional on V may be more transportable

types: additive/multiplicative scale, qualitative (effect in opposite directions)/quantitative, surrogate/causal

calculation:

- *stratify* by V then standardize/IP weight for L,
- L as *matching* factor (ensures positivity, difficult if high-dimensional L)

collapsibility: causal risk difference and ratio are weighted averages of stratum-specific risks, can not be done for odds ratio

interaction chapter 5

causal diagrams chapter 6, include swigs from 7.5 and that one technical point

more on SWIGS p 242ff

confounding chapter 7

selection bias chapter 8

measurement bias chapter 9

random variabilty chapter 10

2 Models

Modeling data are a sample from the target population

estimand:	quantity of interest,	e. g. $\mathrm{E}[Y\|A=a]$
estimator:	function to use,	e. g. $\widehat{\mathrm{E}}[Y\|A=a]$
estimate:	apply function to data,	e. g. 4.1

model: a priori restriction of joint distribution/dose-response curve; *assumption:* no model misspecification (usually wrong)
non-parametric estimator: no restriction (saturated model) = *Fisher consistent estimator* (entire population data → true value)
parsimonious model: few parameters estimate many quantities
bias-variance trade-off:
wiggliness ↑ → misspecification bias ↓, CI width ↑

Variable Selection can induce bias if L includes:

(decendant of) collider:	*selection bias under the null*
noncollider effect of A:	*selection bias under the alternative*
mediator:	*overadjustment for mediators*

temporal ordering is not enough to conclude anything
bias amplification: e.g. by adjusting for an instrument Z (can also reduce bias)

Machine Learning L is high-dimensional
use lasso or ML for IP weighting/standardization
but: ML does not guarantee elimination of confounding and has largely unknown statistical properties
→ **doubly robust estimator:** consistent if bias $< \frac{1}{\sqrt{n}}$
sample splitting: train estimators on training sample, use resulting estimators for doubly robust method on estimation sample (CIs on estimation sample are valid, but n halved)
cross-fitting: do again the other way round, average the two estimates, get CI via bootstrapping
problems: unclear choice of algorithm, is bias small enough?

Super Learning (Van der Laan et al., 2007, 2011)
oracle selector: select best estimator of set of learners Z_i
discrete super learner: select algorithm with smallest cross-validated error (converges to oracle for large sample size)
super learner: improves asymptotically on discrete version
$\mathrm{logit}(Y=1|Z) = \sum_i \alpha_i Z_i$, with $0 < \alpha_i < 1$ and $\sum \alpha_i = 1$
can be cross-validated itself to check for overfitting (unlikely)

2.1 Traditional Methods

Stratification calculate risk for each stratum of L
only feasible if enough data per stratum

Outcome regression chapter 15

instrumental variable estimation chapter 16

causal survival analysis chapter 17 (and technical point 22.3)

2.2 G-Methods

G-Methods *g*eneralized treatment contrasts: adjust for (surrogate) confounders L

- **standardization** two types of g-formula
- **IP weighting** also g-formula
- **g-estimation:** not needed unless longitudinal

Standardization plug-in (or parametric if so) g-formula

$$\mathrm{E}[Y^a] = \overbrace{\mathrm{E}\left[\mathrm{E}[Y|A{=}a, L{=}l]\right]}^{\text{conditional expectation}} = \overbrace{\int \mathrm{E}[Y|L=l, A=a]\, f_L[l]\, dl}^{\text{joint density estimator}}$$

weighted average of stratum-specific risks; unknowns can be estimated non-parametrically or modeled

no need to estimate $f_L[l]$/integrate as empirical distribution can be used: estimate outcome model → predict counterfactuals on whole dataset → average the results (→ CI by bootstrapping)

for discrete L $\mathrm{E}[Y|A=a] = \sum_l \mathrm{E}[Y|L=l, A=a]\Pr[L=l]$

time-varying standardize over all possible $\bar{l}$-histories
simulates joint distribution of counterfactuals $\left(Y^{\bar{a}}, \bar{L}^{\bar{a}}\right)$ for $\bar{a}$
joint density estimator (jde)

discrete: $\mathrm{E}\left[Y^{\bar{a}}\right] = \sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A}=\bar{a}, \bar{L}=\bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$

continuous: $\int f(y|\bar{a}, \bar{l}) \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right) dl$

for *stochastic strategies* multiply with $\prod_{k=0}^{K} f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right)$

estimation (Young et al., 2011; Schomaker et al., 2019)
1. model $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ and $\mathrm{E}\left[Y|\bar{A}=\bar{a}, \bar{L}=\bar{l}\right]$
2. simulate data forward in time:
   at $k=0$: use empirical distribution of L_0 (observed data)
   at $k>0$: set $\bar{A}=\bar{a}$, *draw* from models estimated in 1.
3. calculate mean of $\hat{Y}^{\bar{a}}_{K,i}$ (bootstrap for CI)

iterated conditional expectation (ice)

$\mathrm{E}\left[Y^{\bar{a}}_T\right] = \mathrm{E}\left[\mathrm{E}\left[\mathrm{E}\left[...\mathrm{E}\left[Y_T|\bar{A}_{T-1}{=}\bar{a}_{T-1}, \bar{L}_T\right]...|\bar{A}_0{=}a_0, L_1\right]|L_0\right]\right]$

estimation (Schomaker et al., 2019)
1. model inside out: Q_T=E$\left[Y_T|\bar{A}_{T-1},\bar{L}_T\right]$ to Q_0=E$\left[Q_1|\bar{L}_0\right]$, predict Q_t with $\bar{A}=\bar{a}$ in each step
2. calculate mean of $\hat{Q}^{\bar{a}}_{0,i}$ (bootstrap for CI)

g-null paradox even if the sharp null holds, model misspecification can lead to it being falsely rejected

Proof: for $L_0 \to A_0 \to Y_0 \to L_1 \to A_1 \to Y_1$, $\bar{a}=(a_0,a_1)$

$$\mathrm{E}\left[Y_1^{\bar{a}}\right] \overset{\text{CE}}{=} \mathrm{E}\left[\mathrm{E}\left[Y_1^{\bar{a}}|A_0{=}a_0,L_0\right]\right]$$

(ice)
$$\overset{\text{CE*}}{=} \mathrm{E}\left[\mathrm{E}\left[\mathrm{E}\left[Y_1|\bar{L},\bar{A}{=}\bar{a},Y_0\right]|A_0{=}a_0,L_0\right]\right]$$
$$\overset{\text{LTP}}{=} \mathrm{E}\left[\sum\nolimits_{l_1}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0,y_0\right]\right]$$
$$\overset{\text{LTP}}{=} \sum\nolimits_{l_0}\left[\sum\nolimits_{l_1}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0,y_0\right]\right]\Pr\left[l_0\right]$$

(jde)
$$\overset{\text{sum}}{=} \sum\nolimits_{\bar{l}}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0\right]\Pr\left[l_0\right]$$

CE: conditional expectation; *: exchangeability;
LTP: law of total probability

Marginal Structural Models association is causation in the IP weighted pseudo-population

associational model $\mathrm{E}\left[Y|A\right]=$ causal model $\mathrm{E}\left[Y^a\right]$

step 1: estimate/model $f\left[A|L\right]$ (and $f\left[A\right]$) $\to$ get $(S)W^A$
step 2: estimate regression parameters for pseudo-population
effect modification variables V can be included (e. g. $\beta_0+\beta_1 a+\beta_2 Va+\beta_3 V$; technically not marginal anymore), $SW^A(V)=\frac{f[A|V]}{f[A|L]}$ more efficient than SW^A

Censoring measuring joint effect of A and C

$\mathrm{E}\left[Y^{a,c=0}\right]$ is of interest

standardization $\mathrm{E}\left[Y|A=a\right]=\int \mathrm{E}\left[Y|L{=}l,A{=}a,C{=}0\right]dF_L\left[l\right]$

IP weights $W^{A,C}=W^A\times W^C$ (uses n) or $SW^{A,C}=SW^A\times SW^C$ (uses $n^{c=0}$)

g-estimation can only adjust for confounding, not selection bias $\to$ use IP weights

G-Estimation (additive) structural nested models

$$\operatorname{logit}\Pr\left[A=1|H(\psi^\dagger),L\right]=\alpha_0+\alpha_1 H(\psi^\dagger)+\alpha_2 L$$
$$H(\psi^\dagger)=Y-\psi_\dagger A$$

find $\psi^\dagger$ which renders $\alpha_1=0$; 95 %-CI: all $\psi^\dagger$ for which $p>0.05$
closed-form solution for linear models
derivation: $H(\psi^\dagger)=Y^{a=0}$

$$\operatorname{logit}\Pr\left[A=1|Y^{a=0},L\right]=\alpha_0+\alpha_1 Y^{a=0}+\alpha_2 L$$

$Y^{a=0}$ unknown, but because of exchangeability α_1 should be zero

$$Y^{a=0}=Y^a-\psi_1 a$$

equivalent to $Y^{a=0}=Y^{a=1}-\psi_1$, but using no counterfactuals
structural nested mean model

additive: $\mathrm{E}\left[Y^a-Y^{a=0}|A=a,L\right]=\beta_1 a\,(+\beta_2 aL)$

multiplicative: $\log\left(\frac{\mathrm{E}\left[Y^a|A=a,L\right]}{\mathrm{E}\left[Y^{a=0}|A=a,L\right]}\right)=\beta_1 a\,(+\beta_2 aL)$

multiplicative is preferred if Y always positive, but does not extend to longitudinal case
semi-parametric: agnostic about β_0 and effect of $L\to$ robust ↑
no time-varying: no nesting; model equals marginal structural models with missing β_0,β_3 (unspecified "no treatment")

sensitivity analysis: unmeasured confounding ($\alpha_1\neq 0$) can be examined: do procedure for different values of $\alpha_1\to$ plot α_1 vs. $\psi^\dagger\to$ how sensitive is estimate to unmeasured confounding?
effect modification: add V in both g-estimation equations
doubly robust estimators exist

IP Weighting *i*nverse *p*robability of treatment (g-formula)

$$\mathrm{E}\left[Y^a\right]=\mathrm{E}\left[\frac{I(A=a)Y}{f\left[A|L\right]}\right];W^A=\frac{1}{f\left[A|L\right]};SW^A=\frac{f(A)}{f\left[A|L\right]}$$

unknowns can be estimated non-parametrically or modeled
pseudo-population: everyone is treated & untreated ($L\not\to A$)
FRCISTG *(fully randomized causally interpreted structured graph)*: probability tree for $L\to A\to Y$, can be used to calculate/visualize simulation of values for A
for discrete $\boldsymbol{A,L}$ $f\left[a|l\right]=\Pr\left[A=a,L=l\right]$
estimators: Horvitz-Thompson; Hajek (modified version)
stabilized weights $\boldsymbol{SW^A}$ should have an average of 1 (check!)
$\to$ pseudo-population same size $\to$ CI width ↓

Standardization and IP Weighting are equivalent, ***but*** if modeled, different "no misspecification" assumptions:
standardization: outcome model
IP weighting: treatment model

doubly robust estimators: reduce model misspecification bias, consistent if either model is correct; ***e. g.:***
1. fit outcome regression with variable $R=\begin{cases}+W^A & \text{if } A{=}1\\ -W^A & \text{if } A{=}0\end{cases}$
2. standardize by averaging

2.2.1 Time-varying A

IP Weighting

$$W^{\bar{A}}=\prod_{k=0}^{K}\frac{1}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

$$SW^{\bar{A}}=\prod_{k=0}^{K}\frac{f\left(A_k|\bar{A}_{k-1}\right)}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

Doubly Robust Estimator sequential estimation
1. estimate $\hat{f}\left(A_m|\bar{A}_{m-1},\bar{L}_m\right)$ (e. g. logistic model), use it to calculate at each time m: $\widehat{W}^{\bar{A}_m}=\prod_{k=0}^{m}\frac{1}{\hat{f}\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$ and modified IP weights at m: $\widehat{W}^{\bar{A}_{m-1},a_m}=\frac{\widehat{W}^{\bar{A}_{m-1}}}{\hat{f}\left(a_m|\bar{A}_{m-1},\bar{L}_m\right)}$
2. with $\widehat{T}_{K+1}:=Y$, recursively for $m=K,K-1,...,0$:
   (a) fit outcome regression on $\widehat{T}_{m+1}$ with variable $\widehat{W}^{\bar{A}_m}$
   (b) calculate $\widehat{T}_m$ using the outcome model with $\widehat{W}^{\bar{A}_{m-1},a_m}$
3. calculate standardized mean outcome $\widehat{\mathrm{E}}\left[Y^{\bar{a}}\right]=\mathrm{E}\left[\widehat{T}_0\right]$

valid, if treatment or outcome model correct, or treatment correct until k and outcome otherwise ($k+1$ robustness)

G-Estimation nested equations: for each time k
strutural nested mean models separate effect of each a_k

$$\mathrm{E}\left[Y^{\bar{a}_{k-1},a_k,\underline{0}_{k+1}}-Y^{\bar{a}_{k-1},\underline{0}_{k+1}}|\bar{L}^{\bar{a}_{k-1}}=\bar{l}_k,\bar{A}_{k-1}=\bar{a}_{k-1}\right]=$$
$$a_k\gamma_k\left(\bar{a}_{k-1},\bar{l}_k,\beta\right)$$

calculations

$$H_k\left(\psi^\dagger\right)=Y-\sum_{j=k}^{K}A_j\gamma_j\left(\bar{A}_{j-1},\bar{L}_j,\psi^\dagger\right)$$

function γ_j can be, e. g. constant (ψ_1), time-varying only ($\psi_1+\psi_2 k$), or dependent on treatment/covariate history

$$\text{logit}\Pr\left[A_k = 1 | H_k\left(\psi^\dagger\right), \bar{L}_k, \bar{A}_{k-1}\right] =$$

$$\alpha_0 + \alpha_1 H_k\left(\psi^\dagger\right) + \alpha_2 w_k\left(\bar{L}_k, \bar{A}_{k-1}\right)$$

find α_1 that is closest to zero

closed form estimator exists for the linear case

Censoring $\bar{C}$: monotonic type of missing data

standardization:

$\int f(y|\bar{a}, \bar{c}{=}\bar{0}, \bar{l}) \prod_{k=0}^{K} dF\left(l_k|\bar{a}_{k-1}, c_{k-1}{=}0, \bar{l}_{k-1}\right)$

IP weighting:

$$SW^{\bar{C}} = \prod_{k=1}^{K+1} \frac{1 \cdot \Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0\right)}{\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)}$$

3 Longitudinal Data

Time-Varying Treatments compare 2 treatments
treatment history up to k: $\bar{A}_k = (A_0, A_1, ..., A_k)$
shorthand: always treated $\bar{A} = \bar{1}$, never treated $\bar{A} = (\bar{0})$

static strategy: $g = [g_0(\bar{a}_{-1}), ..., g_K(\bar{a}_{K-1})]$

dynamic strategy: $g = \left[g_0(\bar{l}_0), ..., g_K(\bar{l}_K)\right]$

stochastic strategy: non-deterministic g

optimal strategy is where $\mathrm{E}[Y^g]$ is maximized (if high is good)

Sequential Identifiability sequential versions of

exchangability: $Y^g \perp\!\!\!\perp A_k | \bar{A}_{k-1} \ \forall g, k = 0, 1, ..., K$

conditional exchangeability:

$\left(Y^g, L^g_{k+1}\right) \perp\!\!\!\perp A_k | \bar{A}_{k-1} = g\left(\bar{L}_k\right), \bar{L}^k \ \forall g, k = 0, 1, ..., K$

positivity: $f_{\bar{A}_{k-1}, \bar{L}_k}(\bar{a}_{k-1}, \bar{l}_k) \neq 0 \ \Rightarrow$

$$f_{A_k | \bar{A}_{k-1}, \bar{L}_k}(a_k | \bar{a}_{k-1}, \bar{l}_k) > 0 \ \forall \left(\bar{a}_{k-1}, \bar{l}_k\right)$$

consistency:

$Y^{\bar{a}} = Y^{\bar{a}^*}$ if $\bar{a} = \bar{a}^*$; $\quad Y^{\bar{a}} = Y$ if $\bar{A} = \bar{a}$;

$$\bar{L}^{\bar{a}}_k = \bar{L}^{\bar{a}^*}_k \text{ if } \bar{a}_{k-1} = \bar{a}^*_{k-1}; \qquad \bar{L}^{\bar{a}}_k = \bar{L}_k \text{ if } \bar{A}_{k-1} = \bar{a}_{k-1}$$

generalized backdoor criterion (static strategy): all backdoors into A_k (except through future treatments) are blocked $\forall k$

static sequential exchangeability for $Y^{\bar{a}}$

$$Y^{\bar{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1}, \bar{L}_k \quad \text{for } k = 0, 1, ..., K$$

use SWIGs to visually check d-separation

time-varying confounding $\mathrm{E}[Y^{\bar{a}} | L_0] \neq \mathrm{E}[Y | A = \bar{a}, L_0]$

Treatment-Confounder Feedback $A_0 \to L_1 \to A_1$: an unmeasured U influencing L_1 and Y turns L_1 into a collider; traditional adjustment (e. g. stratification) biased: use g-methods

g-null test sequential exchangeability & sharp null true $\Rightarrow$ $Y^g = Y \ \forall g \quad \Rightarrow \quad Y \perp\!\!\!\perp A_0 | L_0$ & $Y \perp\!\!\!\perp A_1 | A_0, L_0, L_1$; therefore: if last two independences don't hold, one assumption is violated

g-null theorem: $\mathrm{E}[Y^g] = \mathrm{E}[Y]$, if the two independences hold ($\Rightarrow$ sharp null: only if strong faithfulness (no effect cancelling))

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If no citation is given, the information is taken from the book (Hernán and Robins, 2020)

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