Leiden University Medical Center

Prediction under interventions: why, what and how?

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Why?

In my experience, clinical prediction models seldom have a pure predictive purpose

"The three tasks of data science"

Hernán, Hsu, Healy, Chance 2019
Carlin and Moreno-Betancur, arXiv 2024

Prediction guidelines

PROBAST ‘risk of bias’ tool (Moons et al 2019):

> “Prognostic models can be used to aid decisions about preventive lifestyle changes, therapeutic interventions, or monitoring strategies”

TRIPOD+AI reporting guideline (Collins et al 2024) :

> “Their primary use is to support clinical decision making, such as … initiate treatment or lifestyle changes”

Systematic review in covid-19 prediction models: 64% of papers recommend their model for treatment decision-making

Background. We aimed to clarify the high-risk factors with multivariate analysis and establish a prediction of disease progression, so as to help clinicians to better choose therapeutic strategy.

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system to impact patient care after further validation with externally collected clinical data. Clinical decision support tools for COVID-19 have strong potential to empower healthcare providers to save lives by prioritizing critical care in patients at high risk for adverse outcomes.

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the external validation set. We also developed a web tool to implement our predictive model. Clinicians can use this web tool to predict the mortality risk of COVID-19 patients early. For those patients with a relatively higher probability of death (e.g. >40%), more interventions could be adopted at an earlier stage by clinicians.

Prosepe et al, Front Epid 2022 (based on review by Wynants et al 2020)

Accurate predictions -> improvement in treatment decisions?

Risk/benefit profile of treatments may vary according to underlying risk:

low risk patients may not need treatment

high risk patients should be treated

But what do we mean by ‘underlying risk’?

- risk without ever being treated?
- the risk under current treatment strategies?
- often unspecified

Why is this a problem?

Hilden and Habbema (1987):

“Prognosis cannot be divorced from contemplated medical action, nor from action to be taken by the patient in response to prognostication.”

In data used for development/evaluation of prediction models, some patients already received the treatment, which affected their outcomes

If we are not clear about the role of those treatments, how can these predictions support decisions in new patients?

Let’s look at three examples where things go wrong

Example 1: ignoring treatment during model development

Algorithm for mortality risk in patients with pneumonia[1,2]

- Low risk patient -> treated as outpatient
- High risk patient -> admit to hospital

Asthma patients had historically lower mortality risk due to effective treatments received in hospital

The model trained on historical data suggested that patients with asthma could be treated as outpatients -> potentially unsafe

Prediction paradox: predictions change treatment decisions which in turn invalidates predictions[3,4,] also referred to as *performative* predictions

[1]Cooper et al 1997, [2]Caruana et al 2015, [3]Peek et al 2017, [4]Lenert et al 2019

Example 2: using treatment as covariate

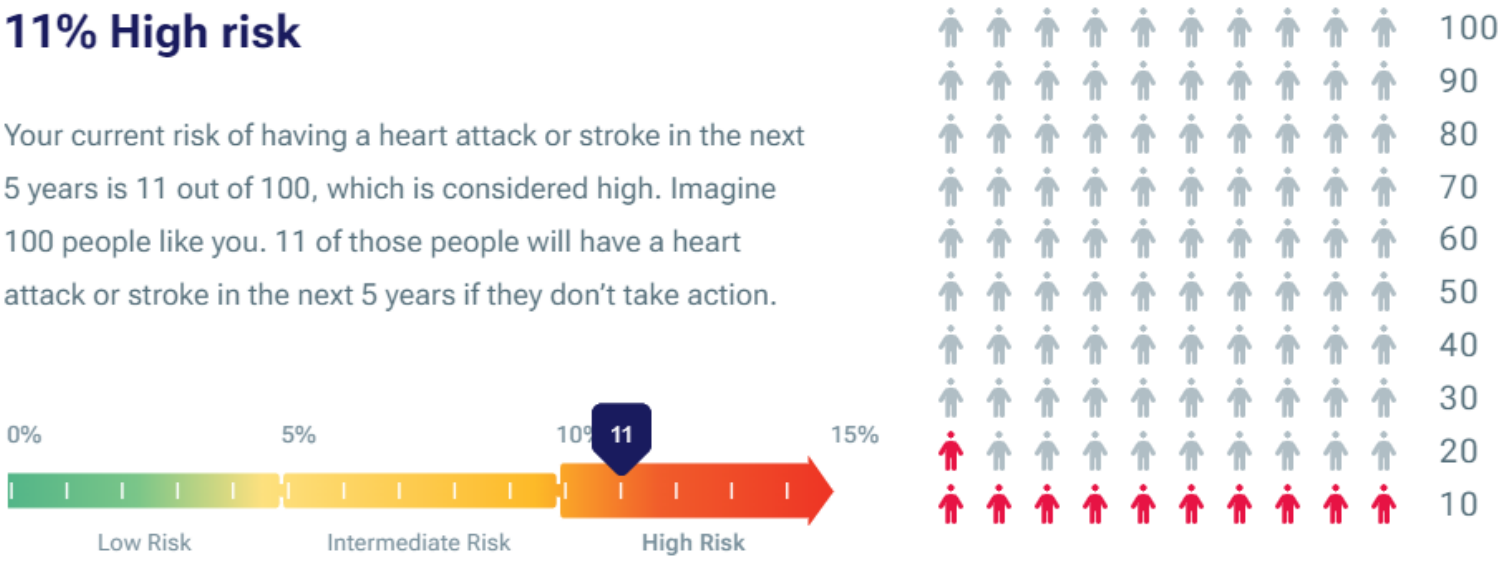
PREDICT equations assessing risk of cardiovascular disease for primary care patients (development cohort n = 400,000, New Zealand)

	Women	Men
Smoking		
Non-smoker	1	1
Ex-smoker	1·09 (1·01–1·18)	1·08 (1·02–1·14)
Smoker	1·86 (1·73–2·00)	1·66 (1·57–1·75)
Family history of premature cardiovascular disease	1·05 (0·97–1·12)	1·14 (1·08–1·21)
Atrial fibrillation	2·44 (2·12– 2·81)	1·80 (1·62–2·00)
Diabetes	1·72 (1·61–1·85)	1·75 (1·66–1·85)
SBP per 10 mm Hg*	1·15 (1·12–1·17)	1·18 (1·16–1·20)
TC/HDL per 1 unit	1·13 (1·11–1·15)	1·14 (1·12–1·15)
Medications at index assessment		
Taking blood pressure lowering medication	1·40 (1·31–1·50)	1·34 (1·27–1·42)

Pylypchuk et al 2018

Example 2: using treatment as covariate

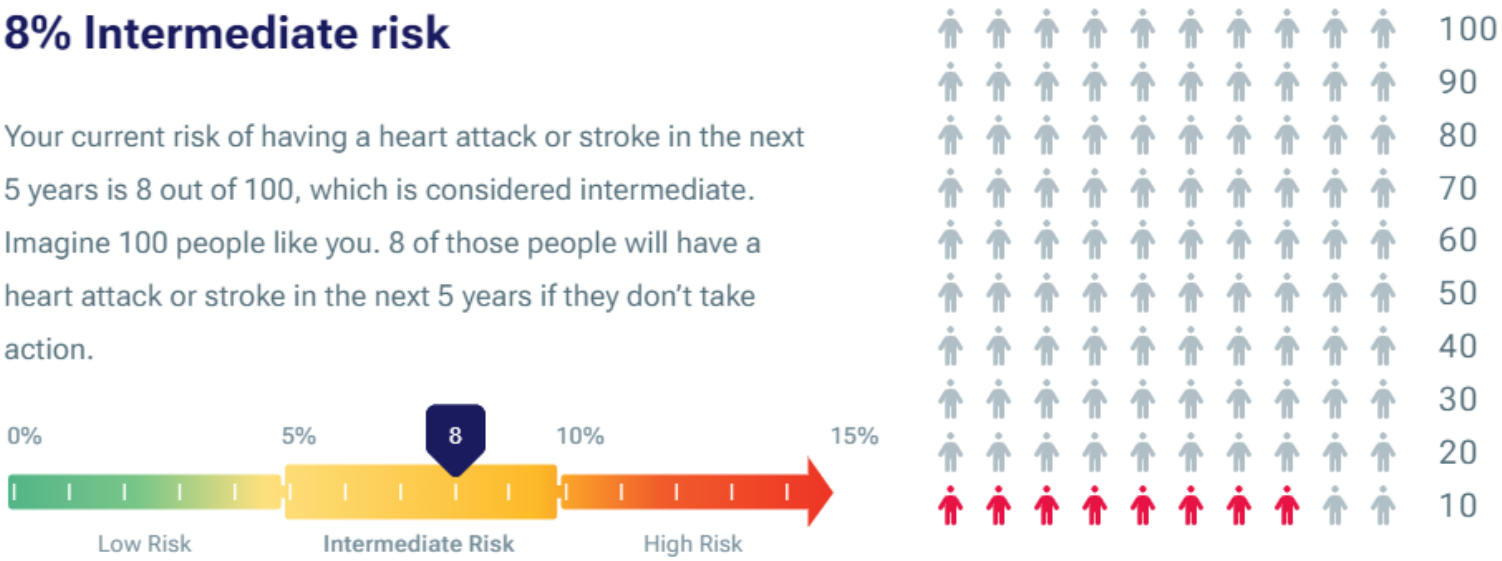
75 year old female, current smoker, SBP 120, TC/HDL 1.1, no comorbidities,
when using blood pressure lowering medication:



https://www.cvdcheck.org.au/calculator

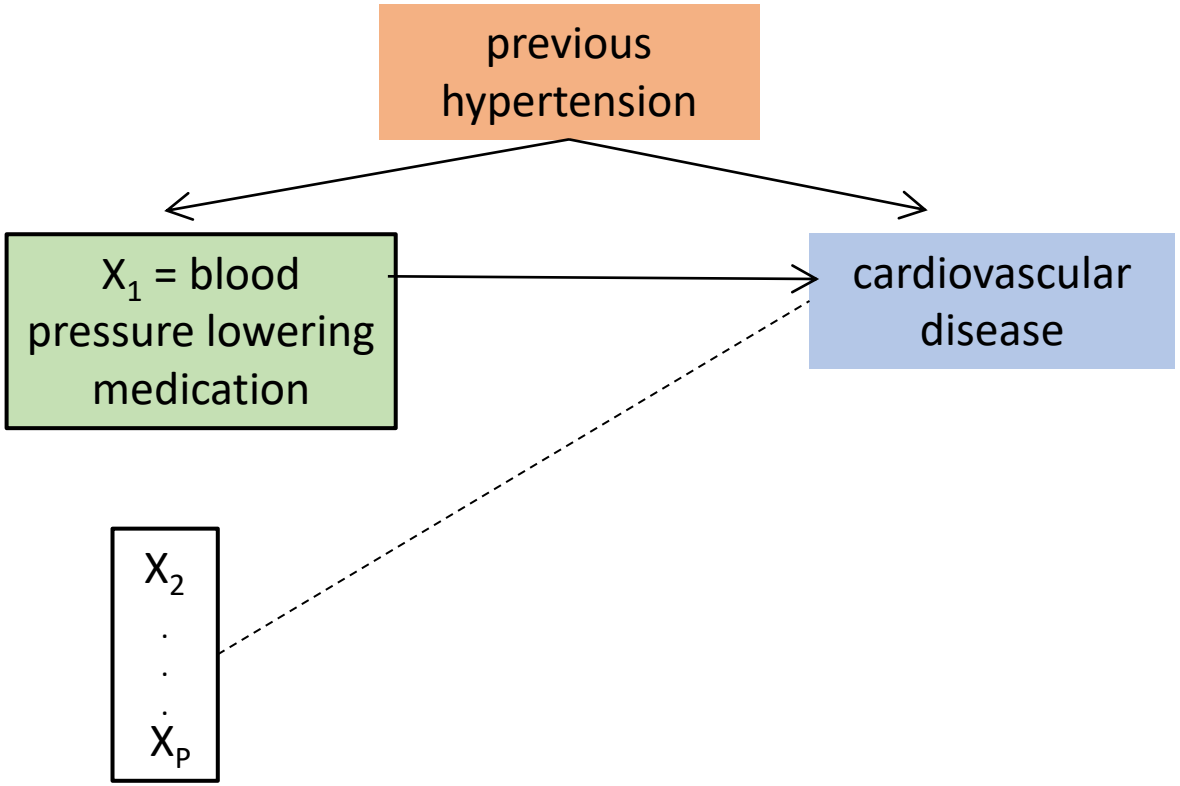
Example 2: using treatment as covariate

75 year old female, current smoker, SBP 120, TC/HDL 1.1, no comorbidities, when NOT using blood pressure lowering medication:



https://www.cvdcheck.org.au/calculator

Example 2: using treatment as covariate



Other causal issues such as mediation, colliding etc. may also play a role[1,2,3]

[1]Van Geloven et al 2024
[2]Westreich and Greenland 2013
[3]Carlin and Moreno-Betancur 2024

Example 3: restricting the development data based on treatment

Instead of using ‘blood pressure medication’ as covariate, select only patients not using it during model development

Problem solved?

No. Just another way of conditioning on treatment

Systematic review on studies predicting mortality for ECMO (heart/lung machine)[1]

-> all 58 studies exclusively included patients who were already on ECMO

-> unfit to support decision on whether to initiate ECMO in individual patients

-> still, 11 / 58 studies wrote this was their primary aim

[1]Pladet et al 2023

What?

Predictions under interventions

1. Formulate a prediction estimand aligned to the targeted treatment decision

2. Assess causal assumptions and estimate accordingly

3. Evaluate predictive performance against outcomes under interventions

4. Assess the impact of using the prediction model on patient outcomes

1. Formulate a prediction estimand aligned to the targeted treatment decision

Prediction estimand[1,2]:

- Population
- Moment(s) of intended use of prediction model
- Outcome and prediction horizon
- Predictor(s) X
- **Intervention option**

$E(Y^a \mid X)$, with Y^a the potential outcome under treatment a

Examples;

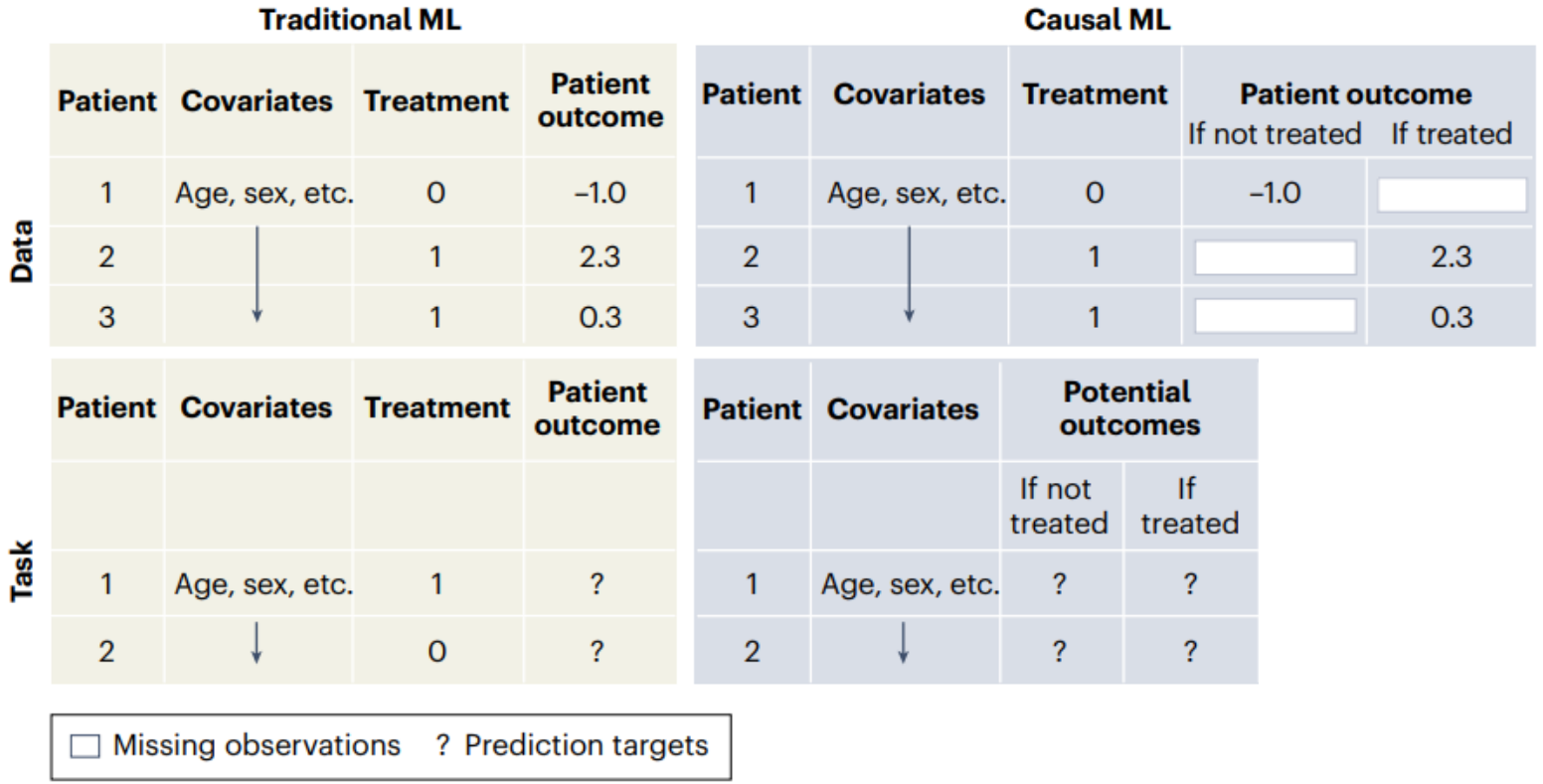
`30-day mortality risk if pneumonia patient with characteristics X is admitted to hospital' (a=1)

`five-year cardiovascular risk if patient with characteristics X decides not to use blood-pressure lowering medication' (a=0)

[1]Van Geloven et al. Eur J Epi 2020

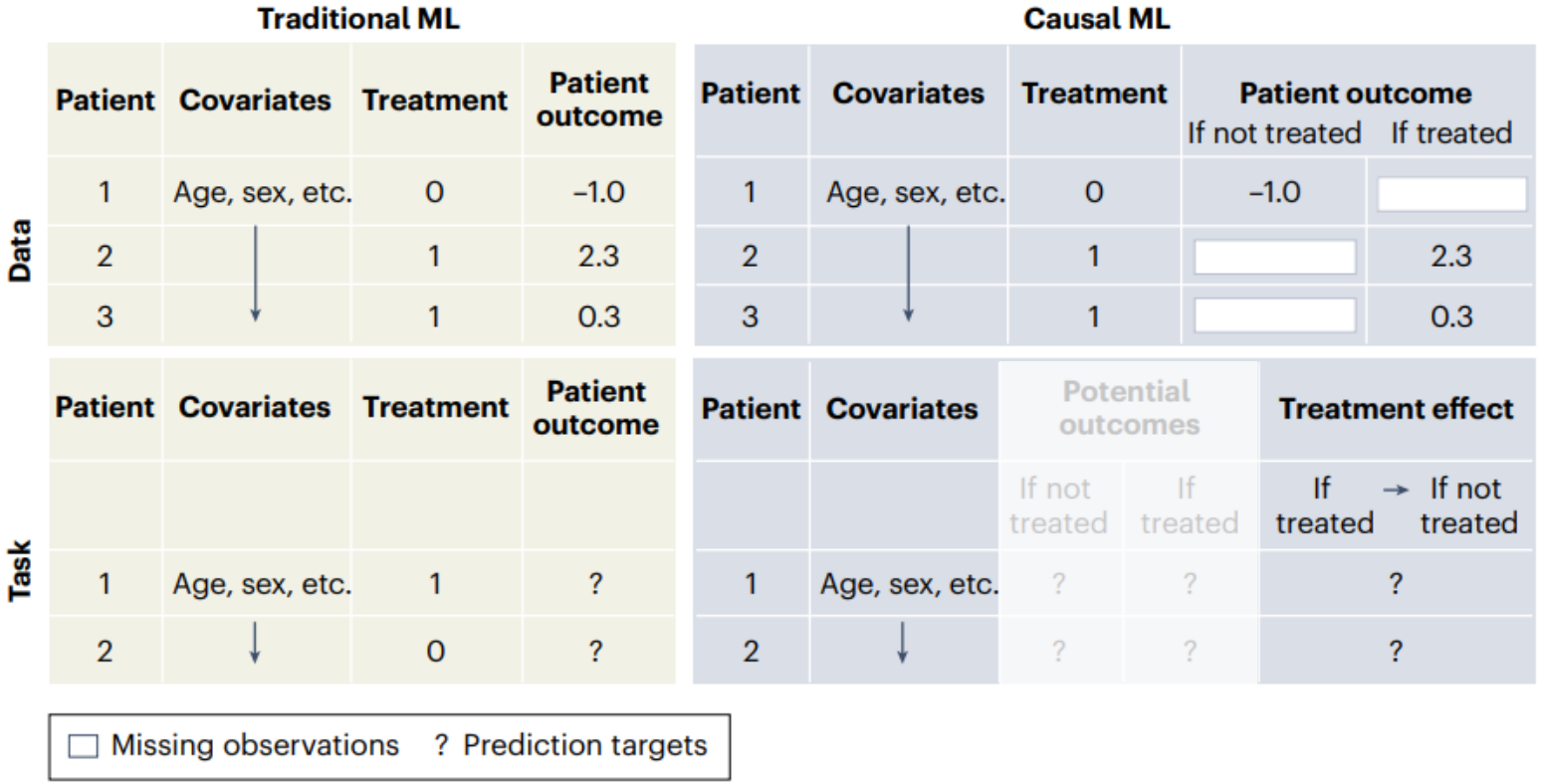
[2]Luijken et al. arXiv 2023

How is this different from usual prediction?

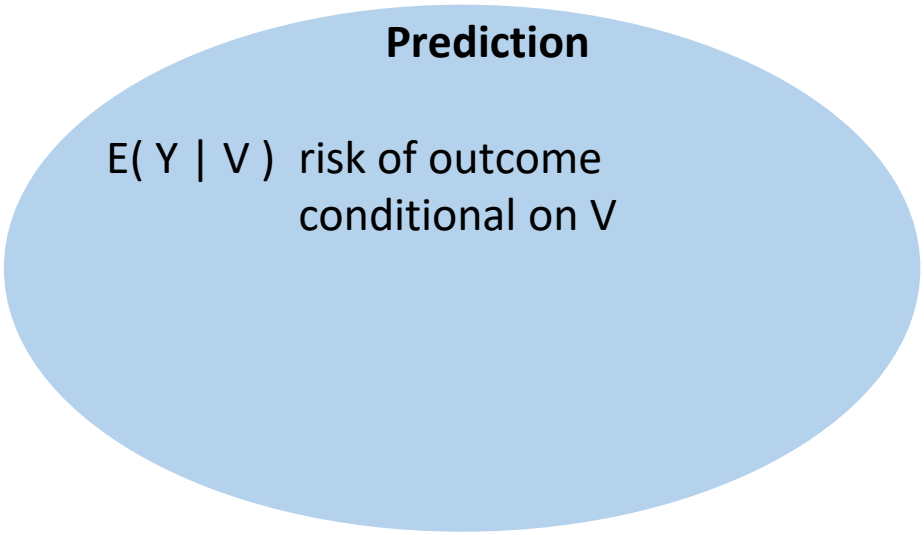


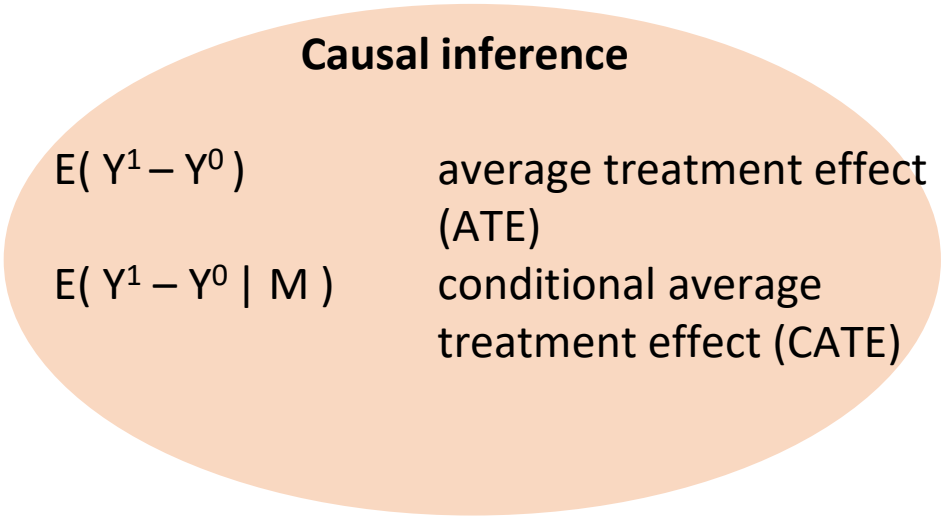
Feuerriegel et al, Nature Medicine 2024

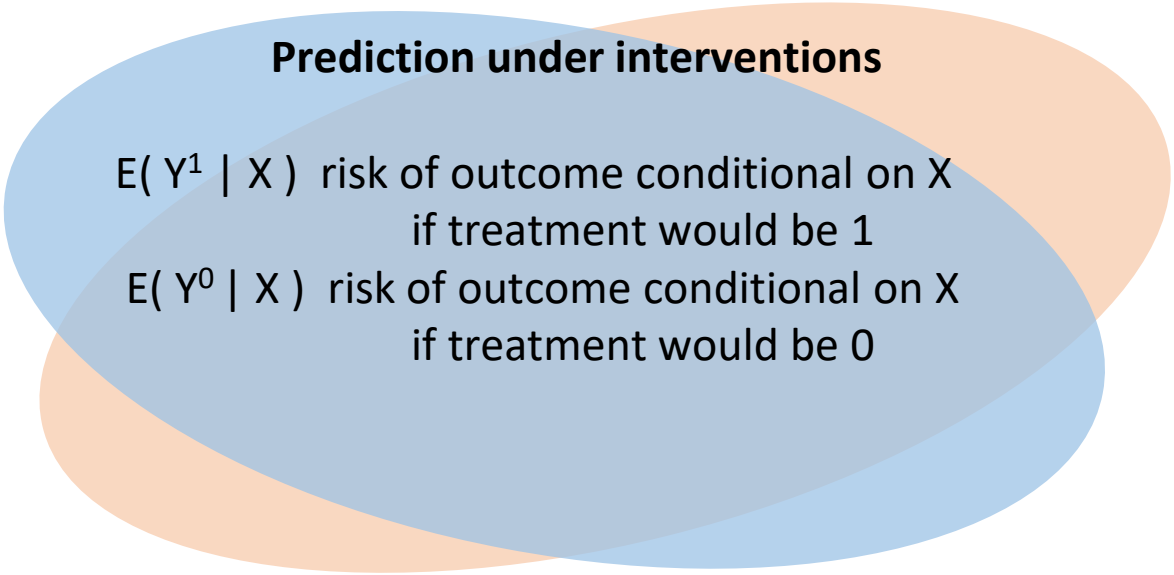
How is this different from usual causal inference?



Feuerriegel et al, Nature Medicine 2024


Prediction
E(Y | V) risk of outcome conditional on V


Causal inference
E(Y1 – Y0) average treatment effect (ATE)
E(Y1 – Y0 | M) conditional average treatment effect (CATE)


Prediction under interventions
E(Y1 | X) risk of outcome conditional on X if treatment would be 1
E(Y0 | X) risk of outcome conditional on X if treatment would be 0

Prediction

$E(Y \mid V)$ risk of outcome conditional on V

V may include anything: no need to worry about confounding, mediation, colliders etc.

Causal inference

$E(Y^1 - Y^0)$ average treatment effect (ATE)

$E(Y^1 - Y^0 \mid M)$ conditional average treatment effect (CATE)

Prediction under interventions

$E(Y^1 \mid X)$ risk of outcome conditional on X if treatment would be 1

$E(Y^0 \mid X)$ risk of outcome conditional on X if treatment would be 0

Prediction

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Causal inference

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M effect modifiers; need to account for confounding and other potential biases

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Prediction under interventions

$E(Y^1 \mid X)$ risk of outcome conditional on X if treatment would be 1

$E(Y^0 \mid X)$ risk of outcome conditional on X if treatment would be 0

X may include prognostic factors and effect modifiers; need to account for confounding and other potential biases

How?

2. Estimating predictions under interventions

- Individual patient data from RCTs, e.g. subgroup analyses / PATH statement[1]
  - + confounding not a problem
  - – often challenged by limited sample size
  - – representativeness (covariate shift)

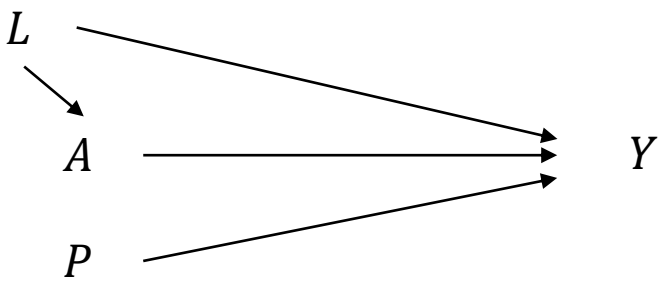
- Combining observational data with treatment effects from published RCT's, e.g., Predict breast cancer
  - + confounding not a problem
  - – other assumptions needed (transportability, mind non-collapsibility)
  - – does not allow treatment heterogeneity

- Observational data
  - + large, representative data sources
  - – main challenge in addressing confounding

[1]Kent et al, Ann Intern Med 2020

Estimating predictions under interventions from observational data

Distinguish observed treatment A, prognostic variables P, confounding variables L and outcome Y



X are the variables in the prediction model, containing (a subset of) P and L

Adding treatment as a variable in the model or selecting data based on A targets:

$$E(Y \mid X, A = a)$$

this only identifies $E(Y^a \mid X)$ under strict assumptions

Identifying assumptions

Conditioning set X solves all confounding and no other (mediation or colliding) issues are introduced, plus conditional positivity and consistency

- conditional exchangeability: $Y^a \perp A \mid X$
- conditional positivity: $0 < \Pr(A = a \mid X) < 1$
- consistency: $Y = Y^a$ if $A = a$

- Note: different from assumptions for average treatment effects, where conditioning would be on L only

Estimating predictions under interventions – time varying treatment

Revisit the estimand:

`five-year cardiovascular risk if patient decides not to use blood-pressure lowering medication'

What does 'decides not to use' mean? Can they start using it tomorrow?

Most interventions are not one-time-only

More informative:

`five-year cardiovascular risk if patient does not take blood-pressure lowering medication during these five years'

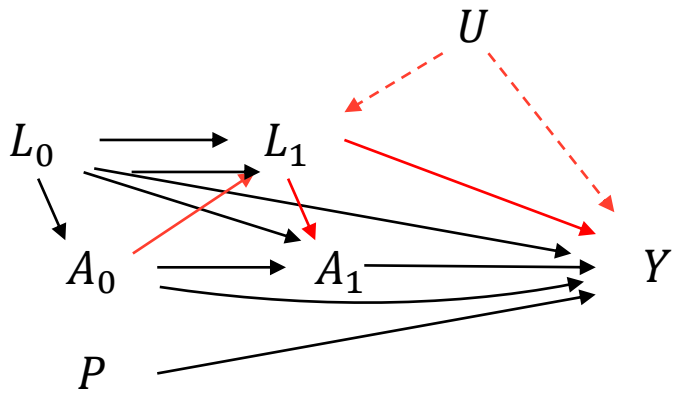
Risk estimand: $E(Y^{\underline{a}_0} \mid X)$, with $\underline{a}_0$ = (0,0,0…)

Additional assumptions needed -> *sequential* conditional exchangeability, positivity and consistency

Estimating predictions under interventions in observational data

– time varying treatment

The decision to go on or off treatment was re-evaluated regularly in the observed data



Baseline variables (P, L_0) -> can be added as predictors in the model

Time varying confounders (L_1) -> more work required

Estimating predictions under interventions from observational data

Lin, L., Sperrin, M., Jenkins, D.A. et al. A scoping review of causal methods enabling predictions under hypothetical interventions. Diagn Progn Res 5, 3 (2021).

Some examples of methods for estimating predictions under intervention with time-varying treatment:

- Marginal structural models with inverse probability weighting[1]
- g-formula[2]
- close-censor-reweight[3]

[1]Sperrin et al 2018, van Geloven et al 2020, Boyer 2023
[2]Dickerman et al 2022
[3]Keogh and van Geloven 2024

3. Evaluate counterfactual predictive performance against outcomes under interventions

Performance metrics (discrimination, calibration, prediction error)

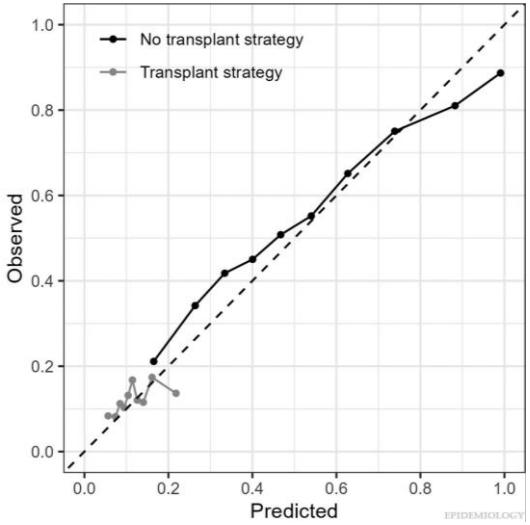
compare *estimated risks* to *observed outcomes* in a test/validation dataset

Both need to have same target -> *observed outcomes* also need to be estimated "under interventions"

This requires modified (counterfactual) performance metrics

3. Evaluate counterfactual predictive performance against outcomes under interventions

For time-to-event outcomes: adjusted metrics proposed in (Keogh and Van Geloven 2024) using artificial censoring + inverse probability weighting



E.g. Calibration plot: predictions against 'observed' proportion of patients with and without treatment

Similar adjustments for c-index, AUCt, Brier score etc

Metrics for binary outcomes proposed in (Boyer et al 2023) using inverse probability weighting, `conditional loss' and doubly robust approach

4. Assess impact of using the prediction model on patient outcomes

- Ideally:
  - (cluster) RCT that compares using the prediction model vs not using the prediction model

- Alternatives
  - subgroup analysis on RCT data that compared treatment options
  - use observational data to mimic the ideal implementation trial

- Impact depends on many things
  - Model accuracy
  - Cut-points suggested for treatment decisions
  - Do people adhere to the suggested cut-points?
  - Is stratifying treatment decisions by risk (cost)-effective?
  - Is the treatment effective?
  - …

Conclusions

Accurate predictions ≠ improvement in treatment decisions

If a predictions model is intended to support treatment decisions:

1. Formulate prediction estimand “under interventions”
2. Estimate based on causal assumptions
3. Evaluate predictive performance “under interventions”
4. Assess the impact of using the prediction model on patient outcomes

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