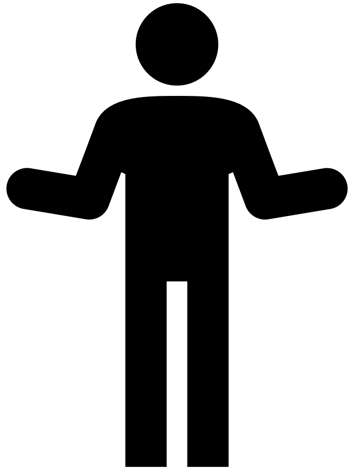
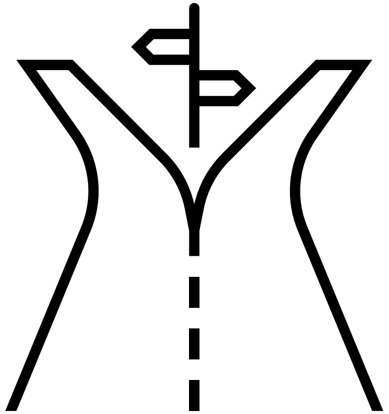
Causal prediction for medical decision making: Methods and practice



Estimands for causal prediction

Nan van Geloven



[Day 2, afternoon]

Many prediction models have a causal purpose

"The three tasks of data science"

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

Systematic review: 64% of covid-19 prediction models suggest their model for 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

“Accurate predictions -> improvement in treatment decisions” is a big misunderstanding

1. predicting ≠ preventing, remember examples day 1: PREDICT, QRISK

2. what are we actually predicting? ← prediction estimands

What are we actually predicting?

We may expect:

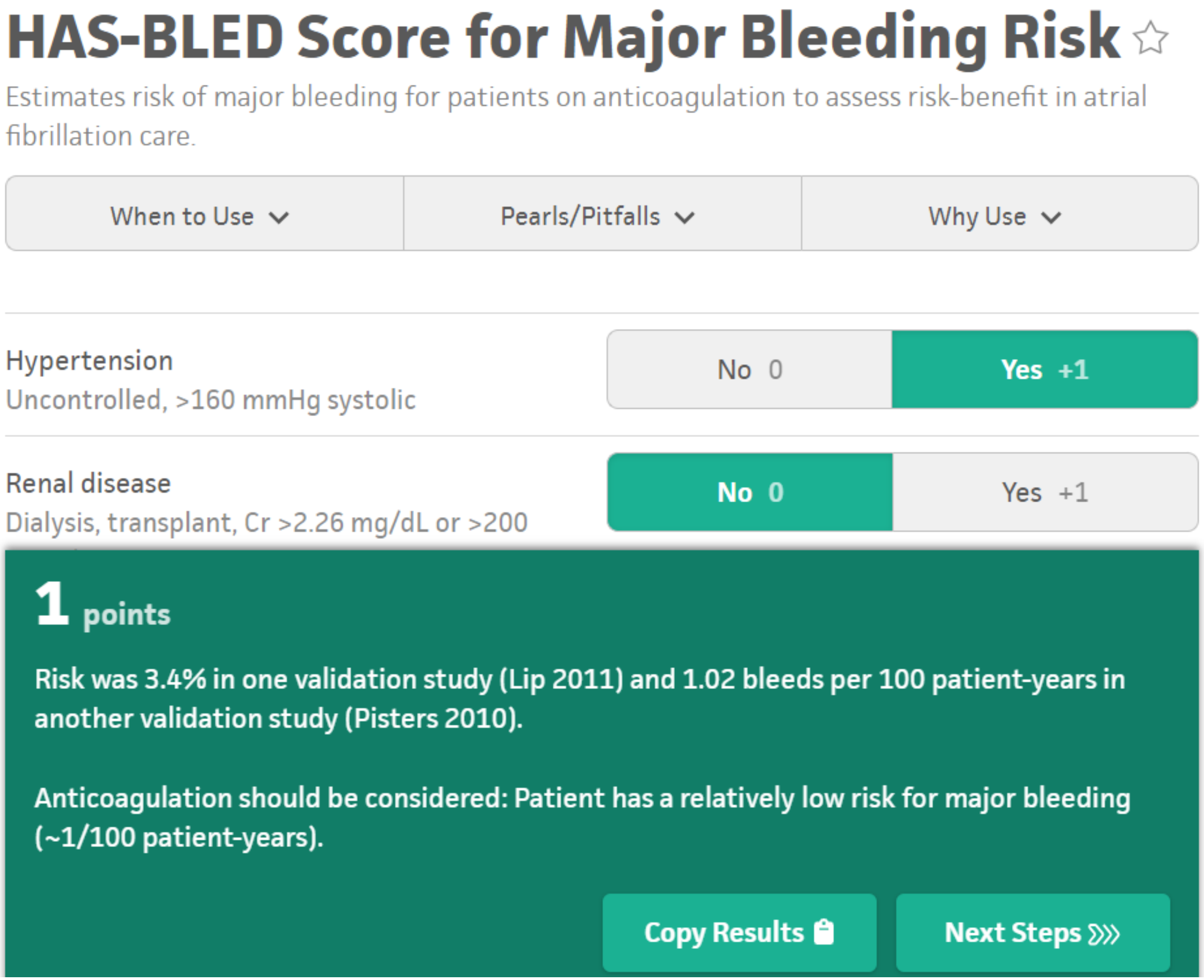
low risk patients may not need treatment

high risk patients should be treated

But what ‘risk’?

- risk without ever being treated?
- the risk under current treatment strategies?
- something else?
- often unspecified in prediction papers!

Example: HAS-BLED score for patients with atrial fibrillation



Example: HAS-BLED score for patients with atrial fibrillation

HAS-BLED Score for Major Bleeding Risk ☆

Estimates risk of major bleeding for patients on anticoagulation to assess risk-benefit in atrial fibrillation care.

When to Use ⌄	Pearls/Pitfalls ⌄	Why Use ⌄

Hypertension Uncontrolled, >160 mmHg systolic	No 0	**Yes +1**
Renal disease Dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L	No 0	**Yes +1**

2 points

Risk was 4.1% in one validation study (Lip 2011) and 1.88 bleeds per 100 patient-years in another validation study (Pisters 2010).

Anticoagulation can be considered, however patient does have moderate risk for major bleeding (~2/100 patient-years).

Copy Results **Next Steps »»**

Example: HAS-BLED score for patients with atrial fibrillation

When to Use | Pearls/Pitfalls | Why Use

Hypertension
Uncontrolled, >160 mmHg systolic
No 0 | Yes +1

Renal disease
Dialysis, transplant, Cr >2.26 mg/dL or >200 μmol/L
No 0 | Yes +1

Liver disease
Cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal
No 0 | Yes +1

3 points

Risk was 5.8% in one validation study (Lip 2011) and 3.72 bleeds per 100 patient-years in another validation study (Pisters 2010).

Alternatives to anticoagulation should be considered: Patient is at high risk for major bleeding.

Copy Results | Next Steps »»

Example: HAS-BLED score for patients with atrial fibrillation

https://www.mdcalc.com/calc/807/has-bled-score-major-bleeding-risk

recommended in European Guideline to inform decisions on anti-coagulation treatment AND 'help address modifiable bleeding risk factors'

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation
(European Heart Journal 2020-doi/10.1093/eurheartj/ehaa612)

HAS-BLED - evidence

2 studies showing reasonable c-statistics

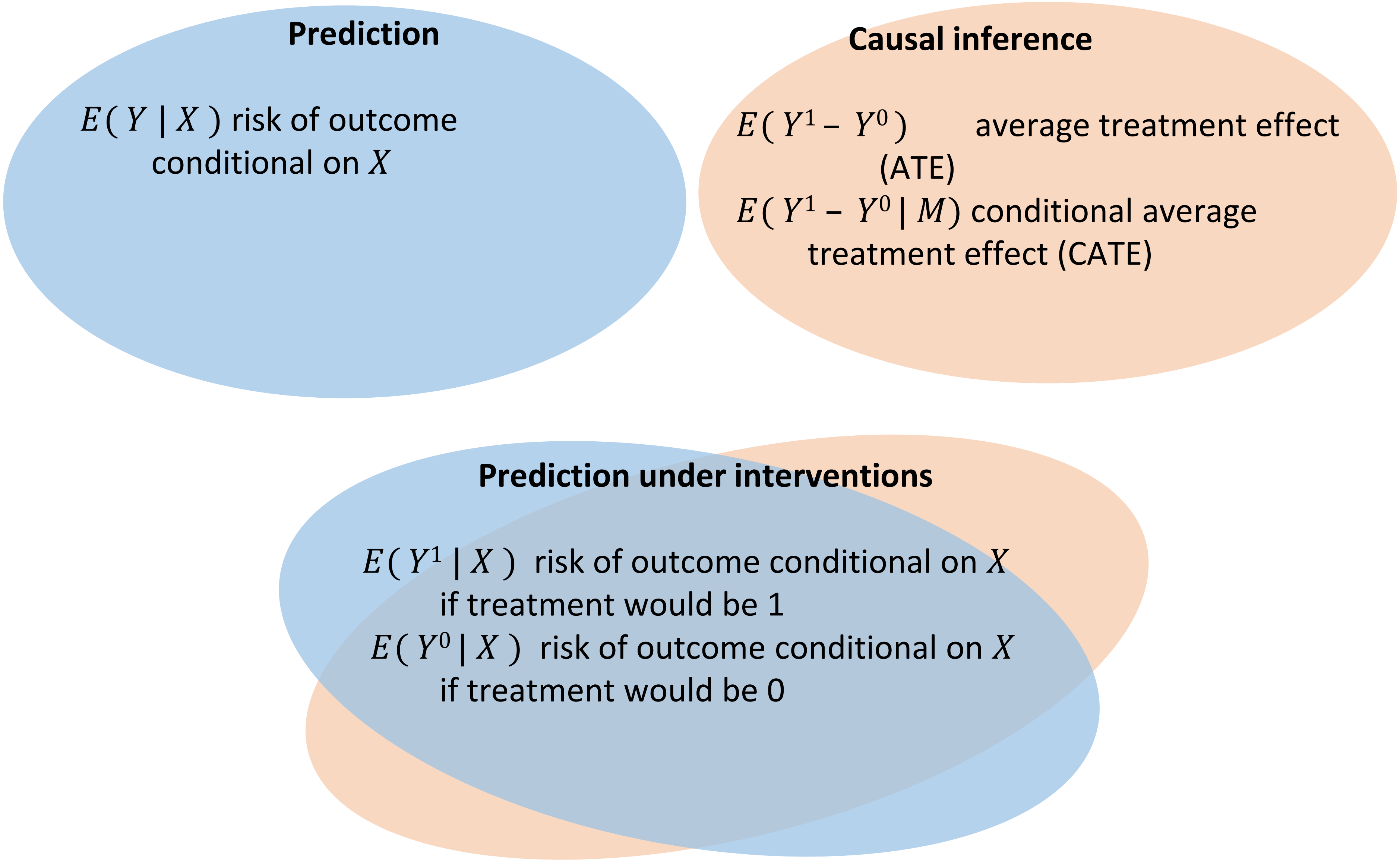
First study included a mix of patients with and without anti-coagulant use[1]

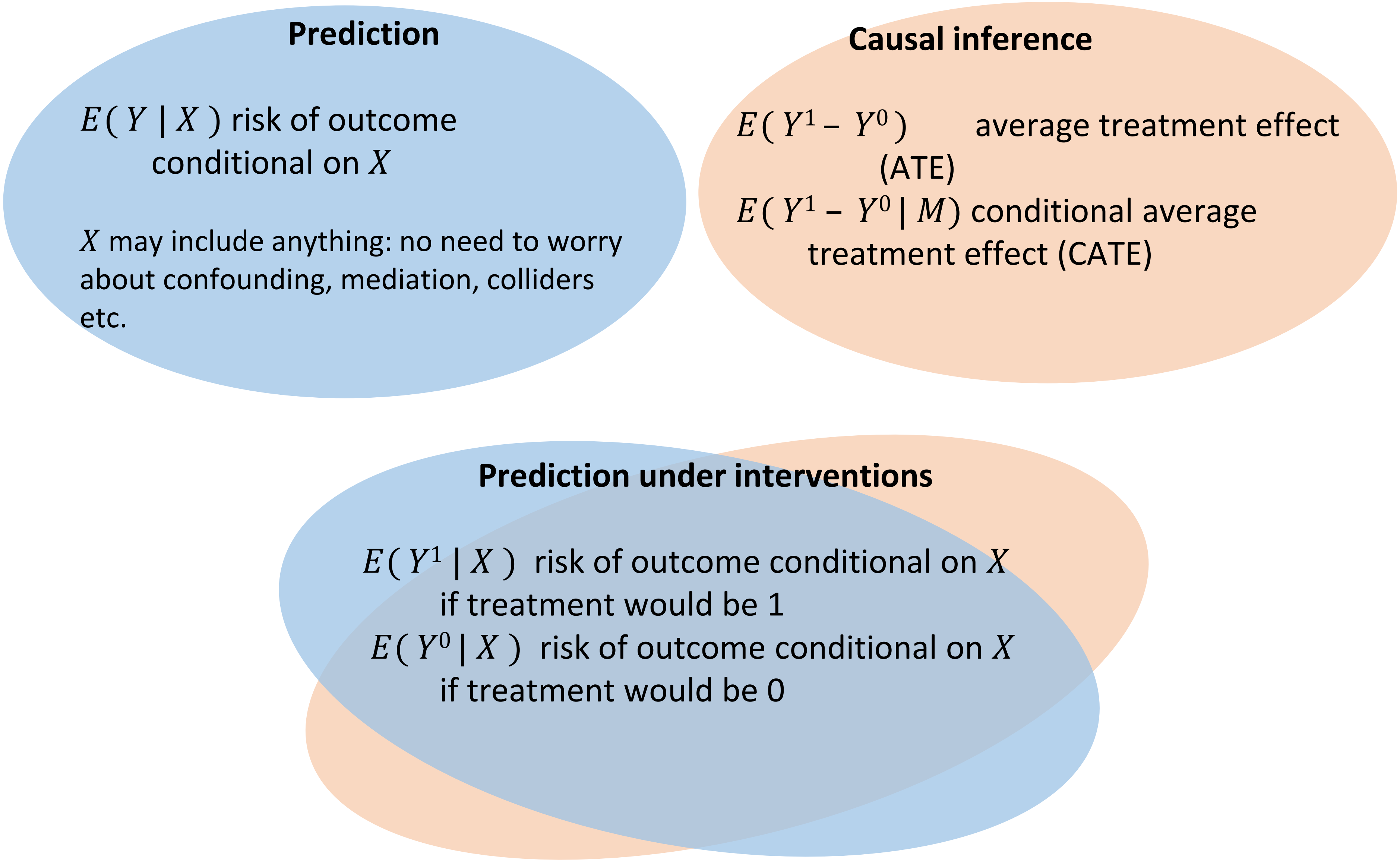
→ Risk under current care $E(Y|X)$

Second study included solely patients treated with anti-coagulants[2]

→ Risk in the (historically) treated $E(Y|X, A = 1)$

[1]Pisters et al 2010
[2]Lip et al 2011


Prediction
$E(Y \mid X)$ risk of outcome conditional on X
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
$E(Y \mid X)$ risk of outcome conditional on X
X may include anything: no need to worry about confounding, mediation, colliders etc.
Causal inference
$E(Y^1 - Y^0)$ average treatment effect (ATE)
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Prediction under interventions
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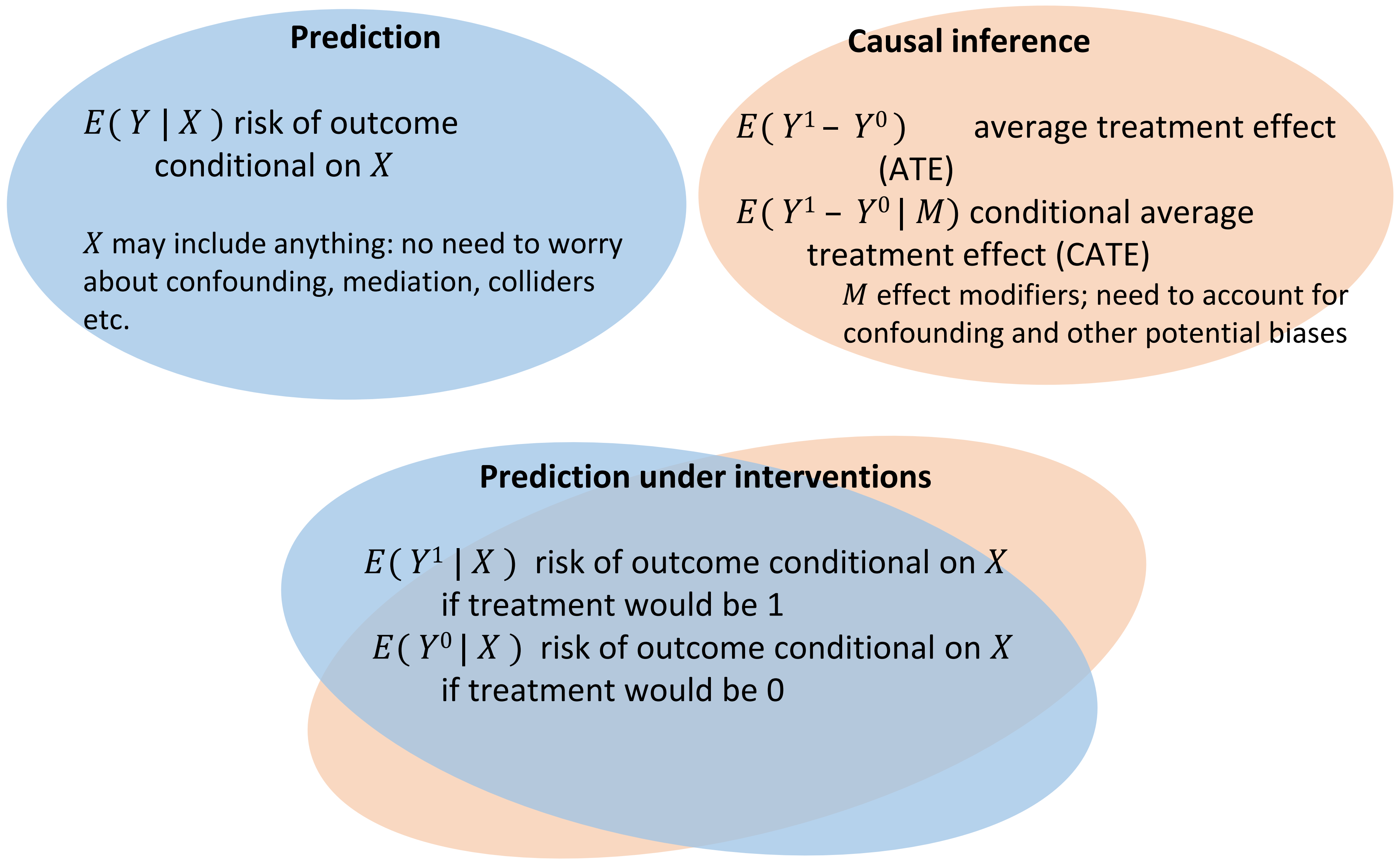
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M effect modifiers; need to account for confounding and other potential biases
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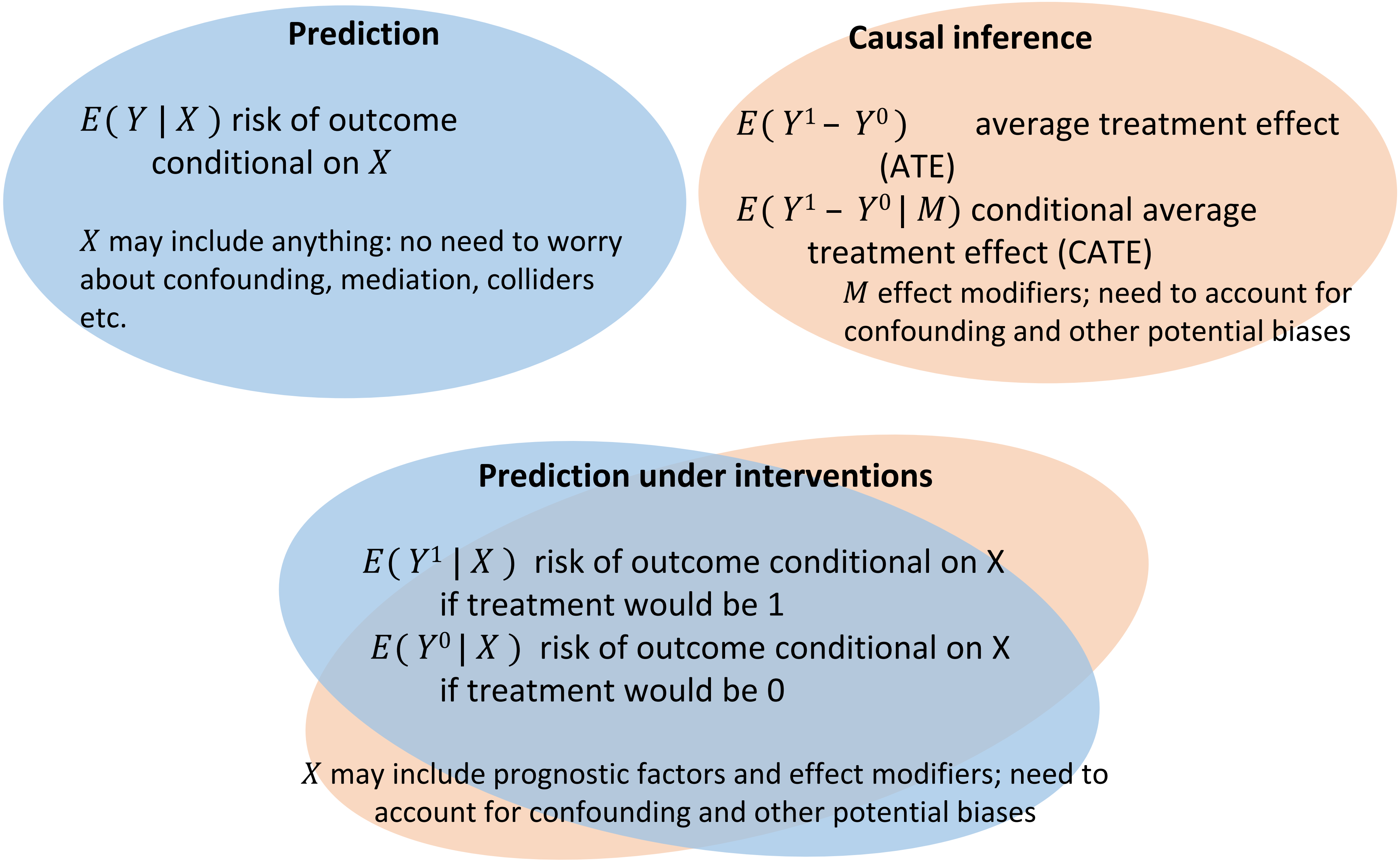
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Prediction under interventions
$E(Y^1 \mid X)$ risk of outcome conditional on X if treatment would be 1
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X may include prognostic factors and effect modifiers; need to account for confounding and other potential biases

How is this different from regular prediction?

Traditional ML

Data

Patient	Covariates	Treatment	Patient outcome
1	Age, sex, etc.	0	−1.0
2	↓	1	2.3
3		1	0.3

Task

Patient	Covariates	Treatment	Patient outcome
1	Age, sex, etc.	1	?
2	↓	0	?

Causal ML

Data

Patient	Covariates	Treatment	Patient outcome	
			If not treated	If treated
1	Age, sex, etc.	0	−1.0	
2	↓	1		2.3
3		1		0.3

Task

Patient	Covariates	Potential outcomes	
		If not treated	If treated
1	Age, sex, etc.	?	?
2	↓	?	?

☐ Missing observations ? Prediction targets

Feuerriegel et al, Nature Medicine 2024

How is this different from regular causal inference?

Traditional ML

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Task

Patient	Covariates	Treatment	Patient outcome
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Causal ML

Data

Patient	Covariates	Treatment	Patient outcome	
			If not treated	If treated
1	Age, sex, etc.	0	−1.0	☐
2		1	☐	2.3
3		1	☐	0.3

Task

Patient	Covariates	Potential outcomes		Treatment effect
		If not treated	If treated	If treated → If not treated
1	Age, sex, etc.	?	?	?
2		?	?	?

☐ Missing observations ? Prediction targets

Feuerriegel et al, Nature Medicine 2024

HAS-BLED – example prediction estimand

Estimand elements	
Target population	Patients with new-onset atrial fibrillation (>18)
Time point of intended use	At first doctor consult after diagnosis
Outcome and prediction horizon	Major bleeding within one year: Y (0 or 1)
Predictors	As in HAS-BLED: X
Treatment option(s)	Start using oral anti-coagulants: $a = 1$

$E(Y^{a=1} \mid X)$, with Y^a the potential outcome under treatment a

“one-year bleeding risk if patient starts anti-coagulants”

Recommendations for estimands for prediction under interventions

Element	What does it mean?	Recommendations
Target population	Persons to whom the prediction model will be applied	Patients for whom all treatment options are possible and for whom a treatment decision is necessary.
Time point of intended use	The moment when the prediction model will be applied	Align time point of intended use with the moment of decision making.
Outcome and prediction horizon	The outcome of interest and the time horizon over which predictions are made	Choose an outcome and time horizon that are relevant to the treatment decision.
Predictors	The clinical and/or demographic patient factors to include in the prediction algorithm	Need to be available at the time of treatment decision making. Need not to be the same as variables needed to adjust for confounding.
Treatment option(s)	The treatment option(s) under which estimates of potential risks are desired	Distinguish between baseline treatments and treatment options that represent longer exposure periods postbaseline.

Prediction estimand for a time-varying treatment

Revisit the HASBLED estimand:

- “one-year bleeding risk if patient starts anti-coagulants”

What does ‘starts’ mean? Can they stop tomorrow? Very few interventions are one time only.

More informative:

- “one-year bleeding risk if patient starts anti-coagulants at baseline and continues this during the year (or until bleeding occurs)”

Risk estimand: $E(Y^{\underline{a}_0} \mid X)$, with $\underline{a}_0$ = (1,1,1...)

This is an example of a *sustained* (continued) treatment

Estimands for sequential prediction

Time point of intended use	At first doctor consult after diagnosis

Revisit the HASBLED estimand again: Is the treatment decision only needed at the first consult?

Decisions may be made repeatedly (or sequentially)

Time point(s) of intended use	The moment**(s)** when the prediction model will be applied	Align time point**(s)** of intended use with the moment**(s)** of decision making.
Outcome and prediction horizon	The outcome of interest and the time horizon over which predictions are made	Outcome and time horizon that are relevant to the treatment decision. **Should horizon align to next prediction moment?**
Treatment option(s)	The treatment option(s) under which estimates of potential risks are desired	Distinguish baseline treatments and longer exposure periods. **Should the exposure period align to next prediction moment?**

Luijken e.a., Biom J 2024

Treatments started after baseline

Patients may add/stop/switch etc other treatments after baseline

4 strategies to handle these (similar to the ICH E9 intercurrent events)

- 'ignore / treatment policy ('intention to treat'), e.g. QRISK
- 'composite', e.g. MACE outcome including bypass surgery
- 'while untreated', e.g. survival while on transplant waiting list
- 'hypothetical', what if it never happens? (similar to sustained)

Van Geloven e.a. Eur J Epid 2020

References

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