SPRING 2023

Spring Meeting Giovani Ricercatori

SID SIIA SIMI SIPREC SISA

Affrontiamo i fattori confondenti:

Propensity score e inferenza causale

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WORKSHOP: "Come approcciarsi ai test statistici: road to Propensity Score"

Outline

- Why propensity score (PS) methods?
- Key concepts in causal inference
- Quantify the causal effect in a simple observational study with one binary confounder
- Estimate the causal effect with multiple measured confounders: PS-based methods
- Conclusions
- Teamwork

Why propensity score (PS) methods?

Multivariate Behavioral Research • *Open Access* • Volume 46, Issue 3, Pages 399 - 424 • May 2011

An introduction to propensity score methods for reducing the effects of confounding in observational studies

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About 6300 citations on Scopus (search done April 2023)

Key idea: mimic characteristics of an RCT

Notation

- A and Y are two binary random variables:
  - **A represents the Treatment/Exposure** (1=exposed,0=not exposed)
  - **Y represents the Outcome**

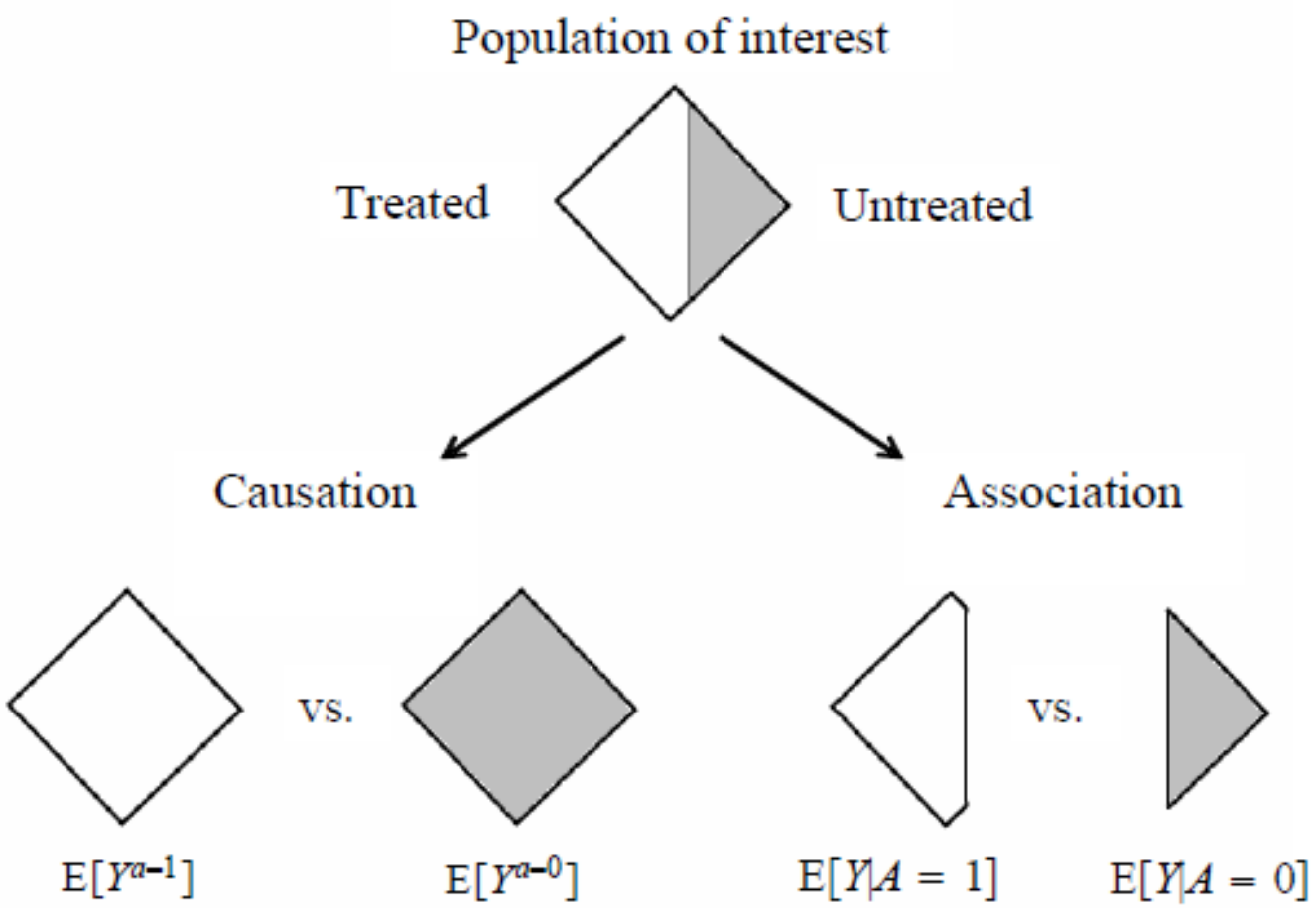
    (1=event 0=no event)

- We also define the **Counterfactual Outcome**:
  - $Y^{a=1}$ outcome Y we would observed under the exposure (a=1)
  - $Y^{a=0}$ outcome Y we would observe in the absence of exposure (a=0)

Definition of causal effect

Causal effect	
INDIVIDUAL 	POPULATION 
A has a causal effect on Y for the subject *i* if: $Y_i^{a=1} \neq Y_i^{a=0}$	A has a causal effect on Y in the population if: $P(Y^{a=1}=1) \neq P(Y^{a=0}=1)$ (or $E[Y^{a=1}] \neq E[Y^{a=0}]$)
$H_0: Y_i^{a=1} = Y_i^{a=0}$	$H_0: P(Y^{a=1}=1) = P(Y^{a=0}=1)$
Generally impossible to measure (exception: cross-over trials)	Under some conditions the **Average Causal Effect (ACE)** could be measured

Causation and association



Average causal effect, ACE
Comparison of **marginal** probabilities

Average effect in subgroups
Comparison of **conditional** probabilities

Association ≠ Causation (example)

Subjects	$Y^{a=0}$	$Y^{a=1}$
1	0	1
2	1	0
3	0	0
4	0	0
5	0	0
6	1	0
7	0	0
8	0	1
9	1	1
10	1	0
11	0	1
12	1	1
13	1	1
14	0	1
15	0	1
16	0	1
17	1	1
18	1	0
19	1	0
20	1	0

Average Causal Effect:

$$P(Y^{a=0}=1)=10/20=0.5$$

$$P(Y^{a=1}=1)=10/20=0.5$$

$$ACE=P(Y^{a=0}=1)-P(Y^{a=1}=1)=0$$

→ **No causal effect of A on Y**

Association ≠ Causation (example)

sub	$Y^{a=0}$	$Y^{a=1}$
1	0	
2	1	
3	0	
4	0	
5		0
6		0
7		0
8		1
9	1	
10	1	
11	0	
12		1
13		1
14		1
15		1
16		1
17		1
18		0
19		0
20		0

→

A	Y
0	0
0	1
0	0
0	0
1	0
1	0
1	0
1	1
0	1
0	1
0	0
1	1
1	1
1	1
1	1
1	1
1	1
1	0
1	0
1	0

Association:

$P(Y=1|A=0)=3/7=0.43$

$P(Y=1|A=1)=7/13=0.54$

$P(Y=1|A=0)-P(Y=1|A=1)\neq 0$

→ **A and Y are not independent**

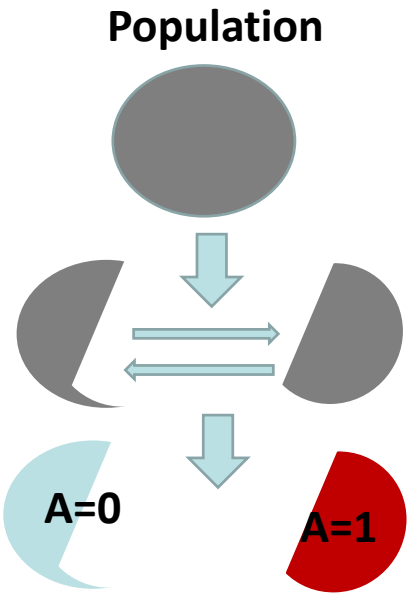
Randomized experiments

- In randomized experiments it is possible to estimate the average causal effect even if we observe only one outcome (either $Y^{a=0}$ or $Y^{a=1}$) for each subject
- Why? Because **exchangeability** holds:

$$P[Y^{a=1}=1|A=1]=P[Y^{a=1}=1|A=0]=P[Y^{a=1}]$$

Conditional probabilities = Marginal probability

$$\Rightarrow \mathbf{Y^a \perp A, \forall\ a}$$



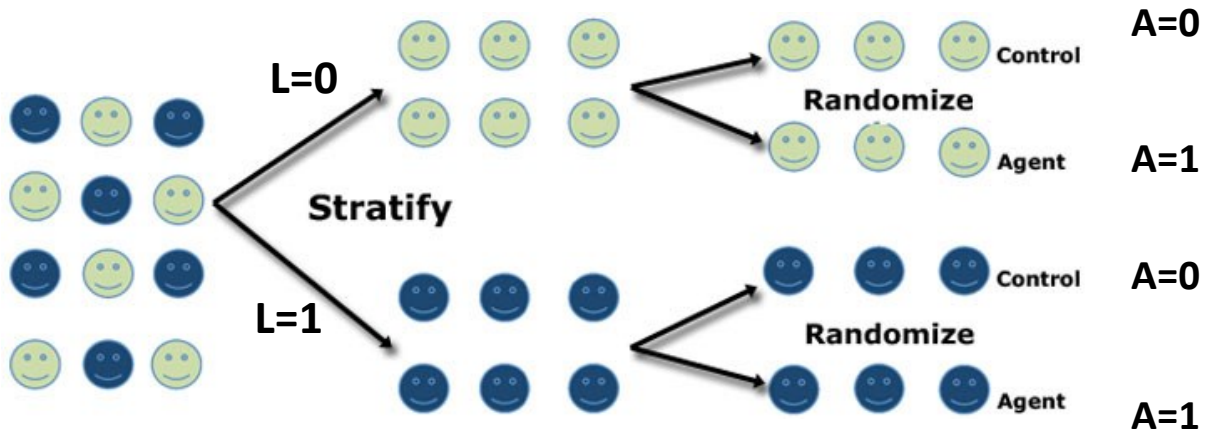
In an «ideal» randomized study:

Association = Causation

$$\mathbf{E[Y|A=1] = E[Y^{a=1}]}$$
$$\mathbf{E[Y|A=0] = E[Y^{a=0}]}$$

NB: In general is not possible to check validity of exchangeability from data

Randomization within strata



- Marginal exchangeability

- Conditional Exchangeability (on L)

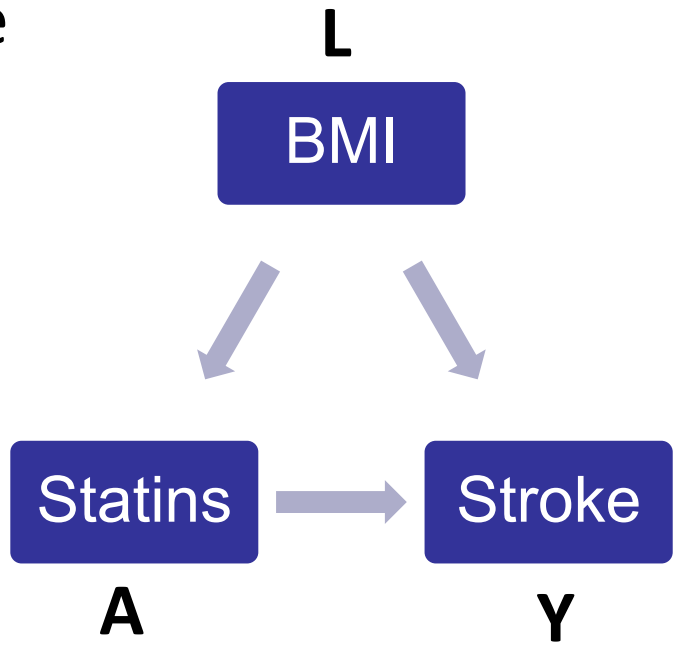
$$Y^a \perp A \mid L, \forall\, a \Leftrightarrow$$

$$E[Y^{a=1} \mid A=1, L=l] = E[Y^{a=1} \mid A=0, L=l] = E[Y^{a=1} \mid L=l]$$

Observational studies

Generally, in observational studies, subject exposed and not exposed are not exchangeable

$$Y^a \not\perp A$$



Common causes of exposure and outcome may exist and be measured (L)

In some situations, conditioned on these characteristics, exchangeability may hold

$$Y^a \perp A \mid L$$

Methods to estimate the causal effect

Context/assumption

- **Studies with randomization within strata**
- **Observational studies with conditional exchangeability**

Aim

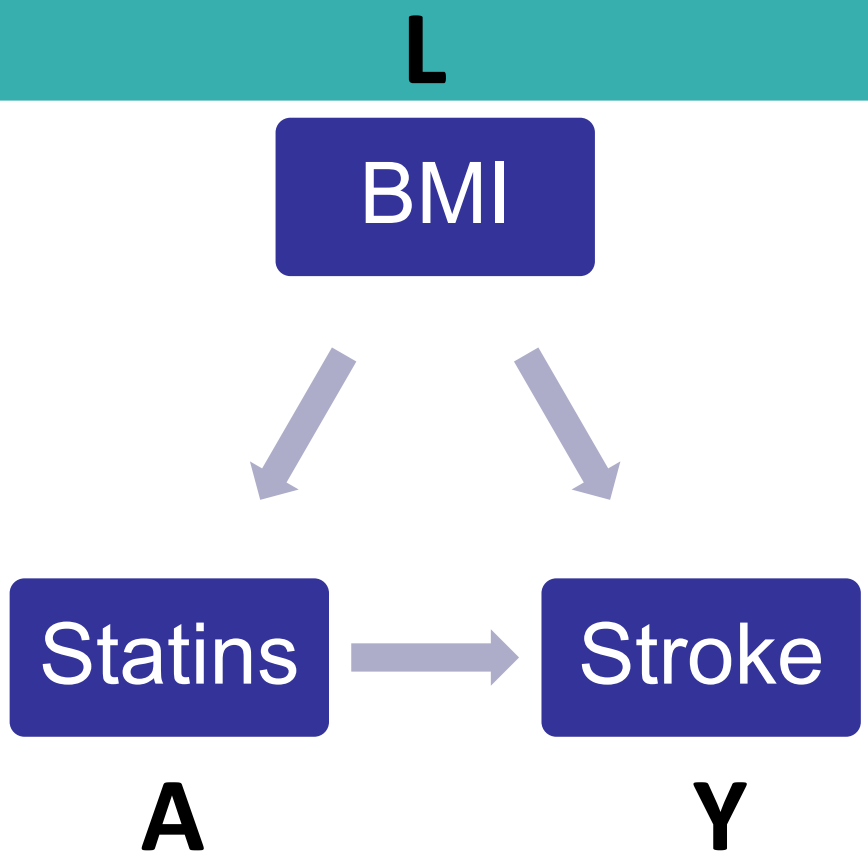
- **Estimate the Average Causal Effect (ACE)**

Methods

- **Stratification (effects within subgroups)**
- **Matching (ATT)**
- **IPW (ATE or ATT)**
- Standardization (aka G-computation)
- …

Toy example

subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0



Assumption:

- **No marginal exchangeability** ✗
- **Conditional Exchangeability (on L)** ✓

Stratification

Separately estimate the effect within the two strata L=0 and L=1

e.g. Relative Risk

$RR_{L=0}$ =

= P(Y=1|L=0,A=1)/P(Y=1|L=0,A=0)

= (2/4) / (1/4) = 2

subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Stratification

Separately estimate the effect within the two strata L=0 and L=1

e.g. Relative Risk

$RR_{L=0}$ =
= P(Y=1|L=0,A=1)/P(Y=1|L=0,A=0)

= (2/4) / (1/4) = 2

$RR_{L=1}$ = P(Y=1|L=1,A=1)/P(Y=1|L=1,A=0)

= (3/9) / (2/3) = 0.5

subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Matching

E.g. matching 1:1

- for each subject not exposed (A=0) in the stratum L=0 randomly match an exposed subject (A=1) in the same stratum L=0.
- Same for L=1.
- Exclude unmatched subjects

subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Matching

In the matched sample, L has the same distribution within exposed and not exposed groups.

Marginal exchangeability ✓

Estimate the average causal effect as in a randomized study

e.g. Relative Risk

$$RR = E[Y^{a=1}]/E[Y^{a=0}]$$

$$= P(Y=1|A=1)/P(Y=1|A=0)$$

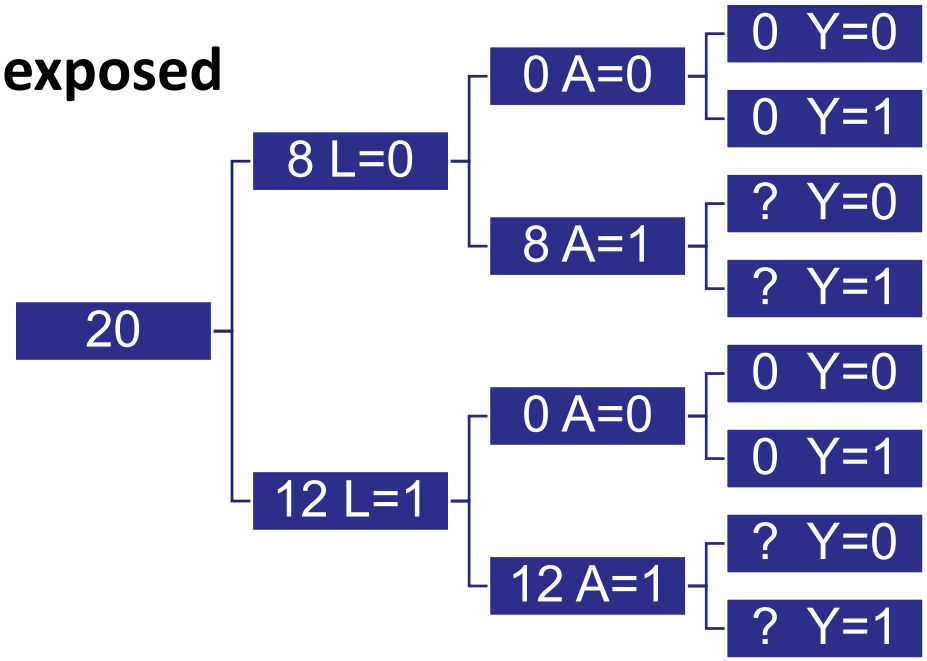
$$= (3/7) / (3/7) = 1$$

subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
14	1	1	1
15	1	1	0
16	1	1	0

Inverse Probabilty Weighting (IPW)

In each stratum, how many events would we expect if subjects are:

1. All exposed



subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Due to conditional exchangeability:

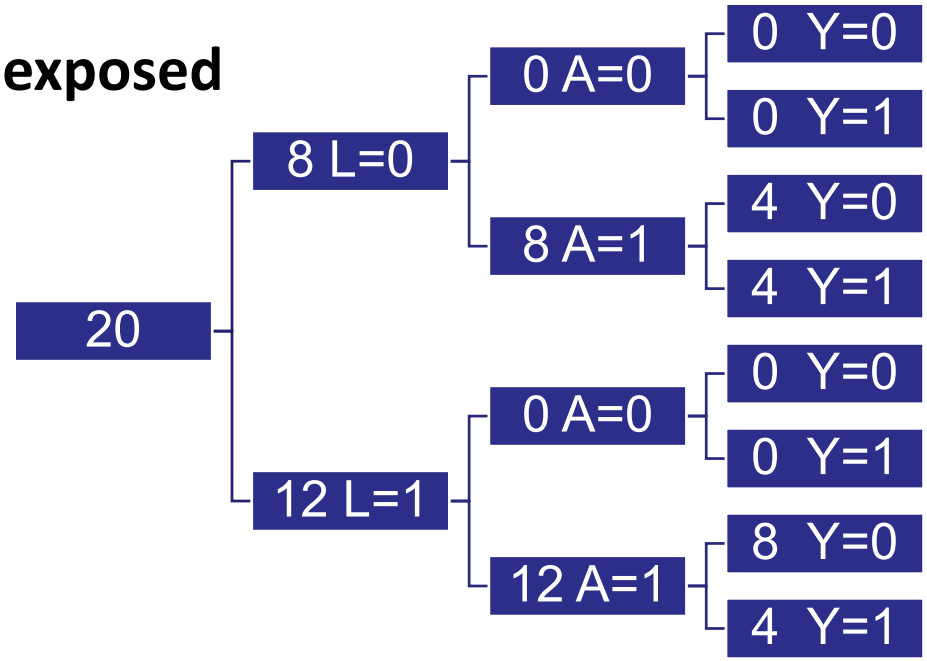
$E(Y^{a=1}|L=1)=P(Y=1|A=1,L=1)$

$E(Y^{a=1}|L=0)=P(Y=1|A=1,L=0)$

Inverse Probabilty Weighting (IPW)

In each stratum, how many events would we expect if subjects are:

1. All exposed



subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Due to conditional exchangeability:

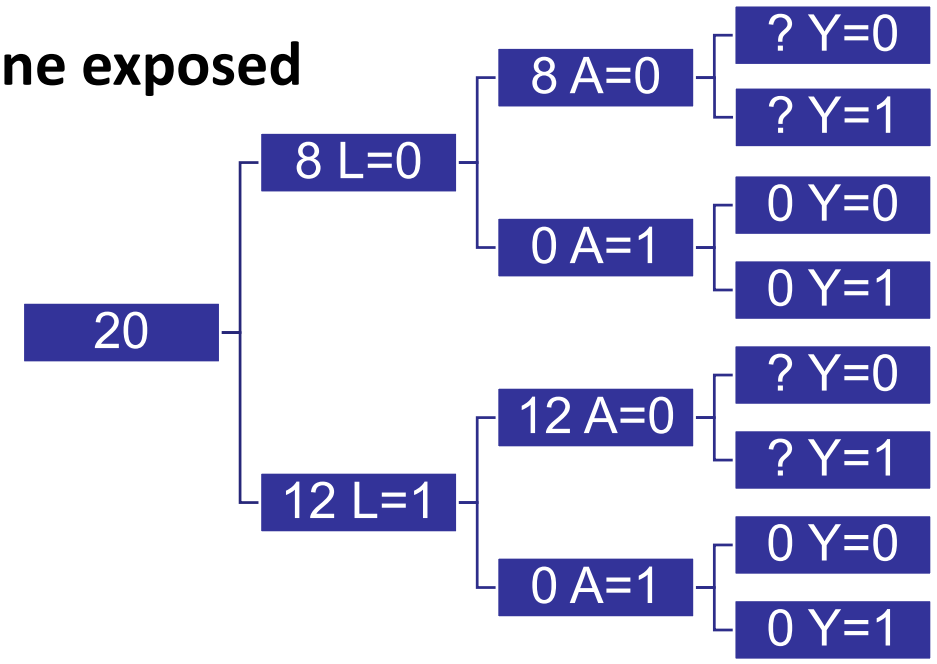
$E(Y^{a=1}|L=1)=P(Y=1|A=1,L=1)$

$E(Y^{a=1}|L=0)=P(Y=1|A=1,L=0)$

Inverse Probabilty Weighting (IPW)

In each stratum, how many events would we expect if subjects are:

2. None exposed



subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Due to conditional exchangeability:

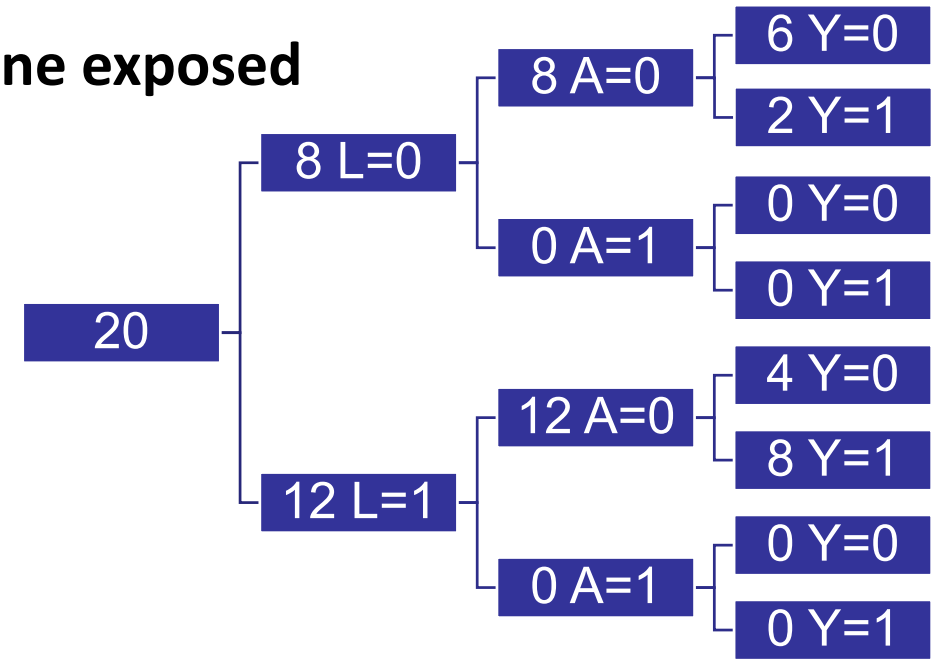
$E(Y^{a=0}|L=1)=P(Y=1|A=0,L=1)$

$E(Y^{a=0}|L=0)=P(Y=1|A=0,L=0)$

Inverse Probabilty Weighting (IPW)

In each stratum, how many events would we expect if subjects are:

2. None exposed



subject	L	A	Y
1	0	0	0
2	0	0	1
3	0	0	0
4	0	0	0
5	0	1	0
6	0	1	0
7	0	1	1
8	0	1	1
9	1	0	1
10	1	0	1
11	1	0	0
12	1	1	1
13	1	1	1
14	1	1	1
15	1	1	0
16	1	1	0
17	1	1	0
18	1	1	0
19	1	1	0
20	1	1	0

Due to conditional exchangeability:

$E(Y^{a=0}|L=1)=P(Y=1|A=0,L=1)$

$E(Y^{a=0}|L=0)=P(Y=1|A=0,L=0)$

Inverse Probabilty Weighting (IPW)

Lets pool together the two samples. In the new *pseudo*-population, L has the same distribution among exposed and non-exposed

Marginal exchangeability ✓

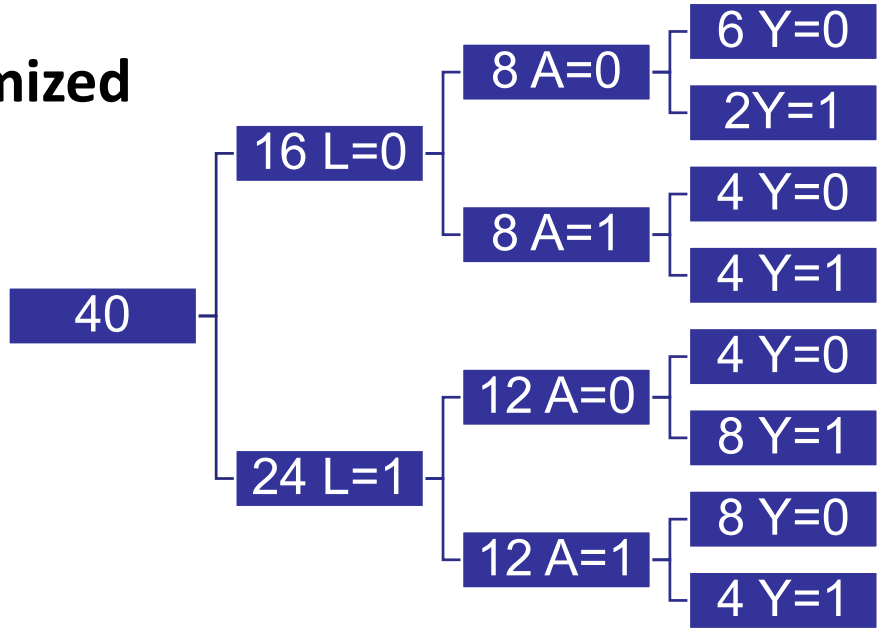
Estimate the ACE as in a randomized study

e.g. Relative Risk

RR = $E[Y^{a=1}]/E[Y^{a=0}]$

=P(Y=1|A=1)/P(Y=1|A=0)

= (8/20) / (10/20) = 0.4/ 0.5 = 0.8



Inverse Probabilty Weighting (IPW)

The *pseudo*-population (size: 2n), can also be created by weighting each individual by $w_A = 1/P(A=a|L=l)$

$P(A=0|L=0)=4/8$
$P(A=1|L=0)=4/8$
$P(A=0|L=1)=3/12$
$P(A=1|L=1)=9/12$

e.g. Relative Risk

$RR = E[Y^{a=1}]/E[Y^{a=0}]$

$=P(Y=1|A=1)/P(Y=1|A=0)$

$= (8/20) / (10/20) = 0.4/ 0.5$
$= 0.8$

subject	L	A	Y	Weights
1	0	0	0	2
2	0	0	1	2
3	0	0	0	2
4	0	0	0	2
5	0	1	0	2
6	0	1	0	2
7	0	1	1	2
8	0	1	1	2
9	1	0	1	4
10	1	0	1	4
11	1	0	0	4
12	1	1	1	1.33
13	1	1	1	1.33
14	1	1	1	1.33
15	1	1	0	1.33
16	1	1	0	1.33
17	1	1	0	1.33
18	1	1	0	1.33
19	1	1	0	1.33
20	1	1	0	1.33

How about dealing with multiple (measured) confounders?

Possible solution: **Propensity Score (PS)**

- For each subject *i*, **PS** is defined as **«the probability of treatment assignment conditional on observed baseline covariates»** (Rosenbaum & Rubin, Biometrika 1983)

$$\mathbf{PS_i = P(A_i = a \mid L_i)}$$

- PS is a measure of **balance**: conditional on PS, the **distribution of covariates** between treatment groups should be **similar**

- Typically estimated by logistic regression, e.g. *PS = P(A = 1 | L)*

$$\boldsymbol{logit\ (PS) = b_0 + b_1L_1 + b_2L_2 + \ldots}$$

- **PS matching**: match patients (e.g. 1:1) with similar PS

Inverse probaility of treatment weighting (IPTW)

- Individuals are weighted for the inverse of the probability of being treated with their actual treatment, given covariates:

$$W_i^{A=a} = \frac{1}{P(A_i = a \mid L_i)}$$

If subject *i* is treated with A=1:

$$W_i = \frac{1}{P(A_i = 1 \mid L_i)} = \frac{1}{PS_i}$$

If subject *i* is treated with A=0:

$$W_i = \frac{1}{P(A_i = 0 \mid L_i)} = \frac{1}{1\text{-}PS_i}$$

- In the weighted population, **marginal exchangeability** is achieved (provided there are no unmeasured confounders).

Conclusions

Issues to consider when using PS methods:

- Positivity assumption
- Absence of unmeasured confouders
- Check balance after PS matching or IPW
- Variable selection for PS model
- Not directly able to correct other type of bias in observational studies: (e.g. selection bias, ecc…)
- More complex settings:
  - Non-binary treatments
  - Time-dependent covariates
- Other causal methods not based on PS: standardization (a.k.a «G-computation»)

Conclusions

Some advantages of PS methods over outcome regression:

- Marginal vs conditional treatment effect
- Easier to estimate some effect measures (risk difference, RR or compare survival curves)
- Easier to check if balance is achieved with PS than to assess if outcome model is correct
- When outcome is rare and sample size is not big regression is limited but not PS

References

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Lavoro a gruppi

Leggere i due articoli ed identificare i seguenti aspetti:

- Tipo di studio (osservazionale/sperimentale?, prospettico retrospettivo?)
- Fattore di esposizione (binario/multicategorico?)
- Endpoint principale (continuo/binario/multicategorico/sopravvivenza?)
- Fattori confondenti (quali? quanti?)
- Metodo PS (matching/IPW?, come è stato stimato il PS?)
- Il bilanciamento dei confondenti è migliorato in seguito all'applicazione del metodo basato sul PS?
- Come è cambiata l'associazione stimata (quale misura di effetto è stata utilizzata?) tra il fattore di esposizione e l'outcome prima vs dopo l'applicazione del metodo basato sul PS?