Measures of Association

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Lecture 5

- descriptive epidemiology (until now)
- analytic epidemiology
  - analysing the association between the suspected causal factor and the disease in the population
  - express the effect size of exposure on the health by absolute and relative association measures
- types
  - clinical trials
  - observational studies

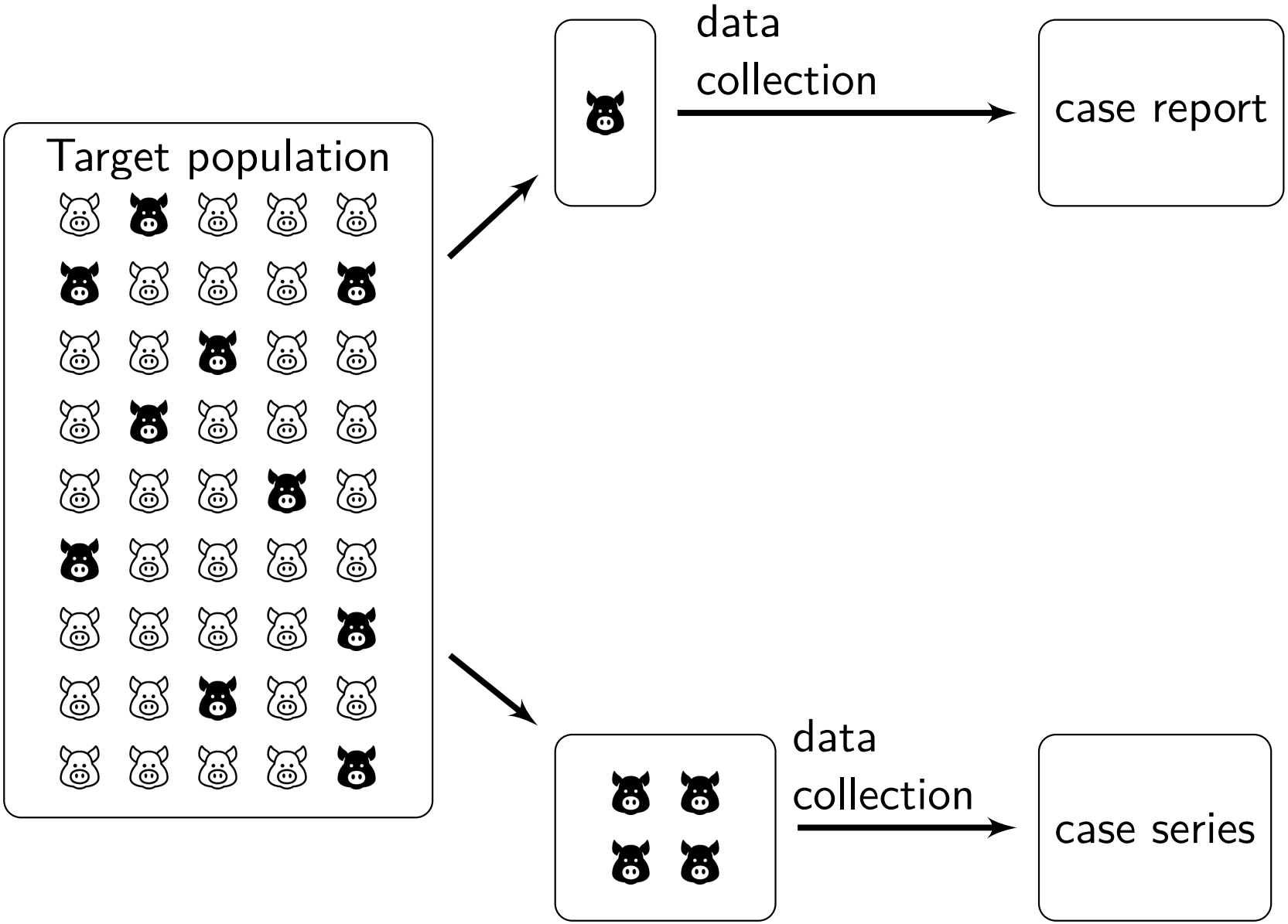
    cross-sectional the animals are sampled without considering health and exposure status beforehand

    case-control the animals are included in the sample based on their health status

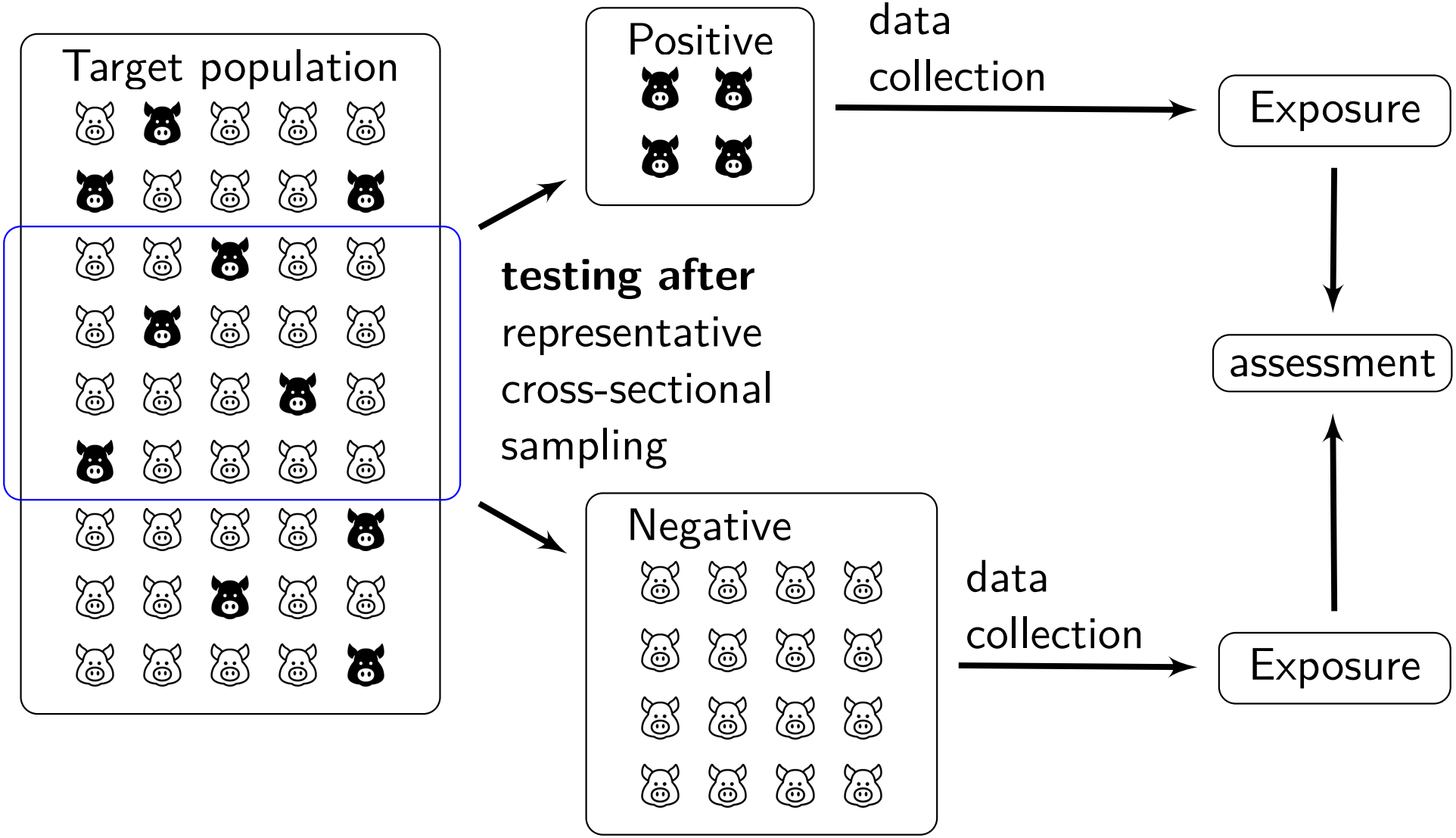
    cohort the animals are included in the sample based on their exposure

    - prospective or retrospective

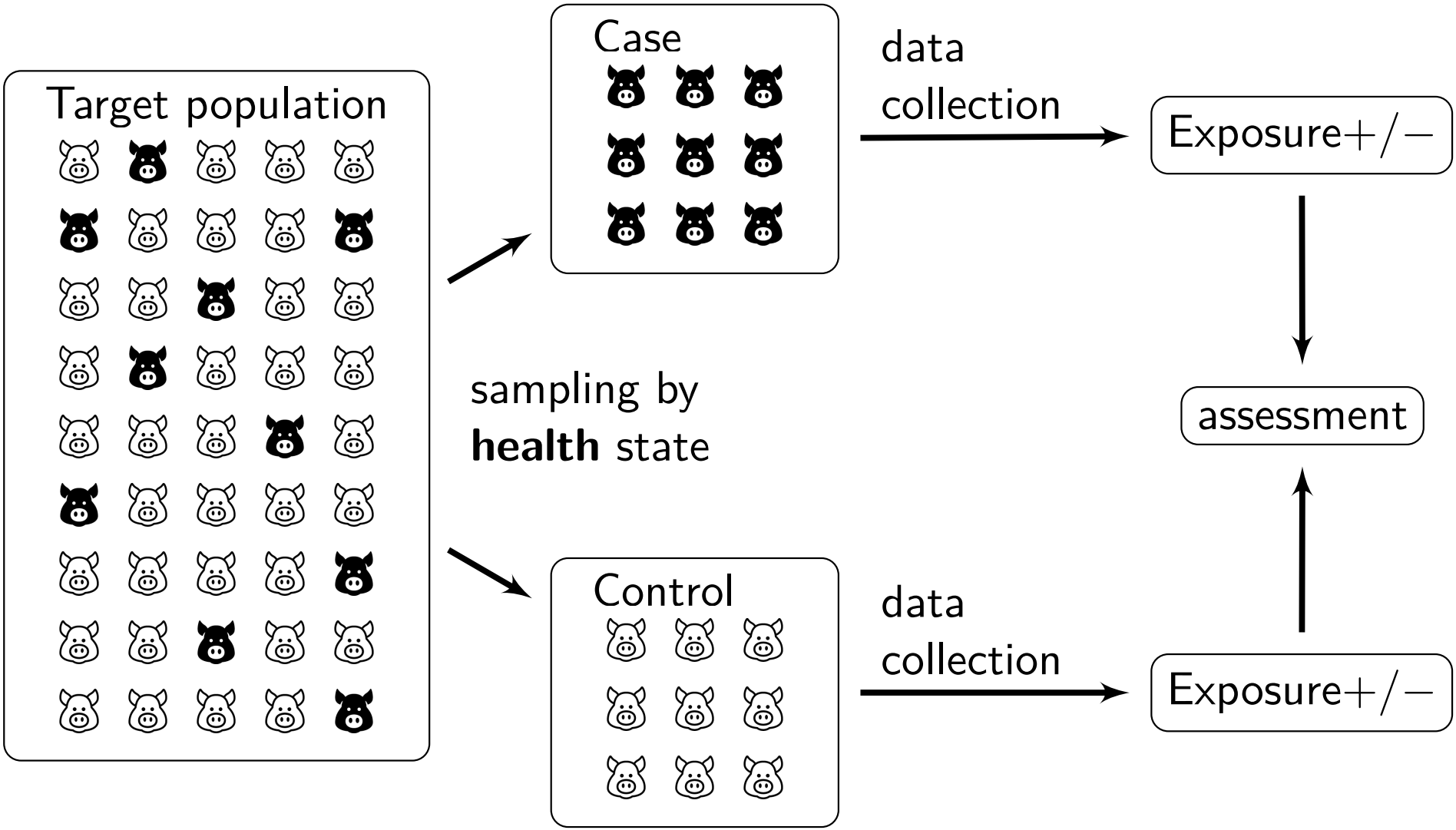
Case reports and case series



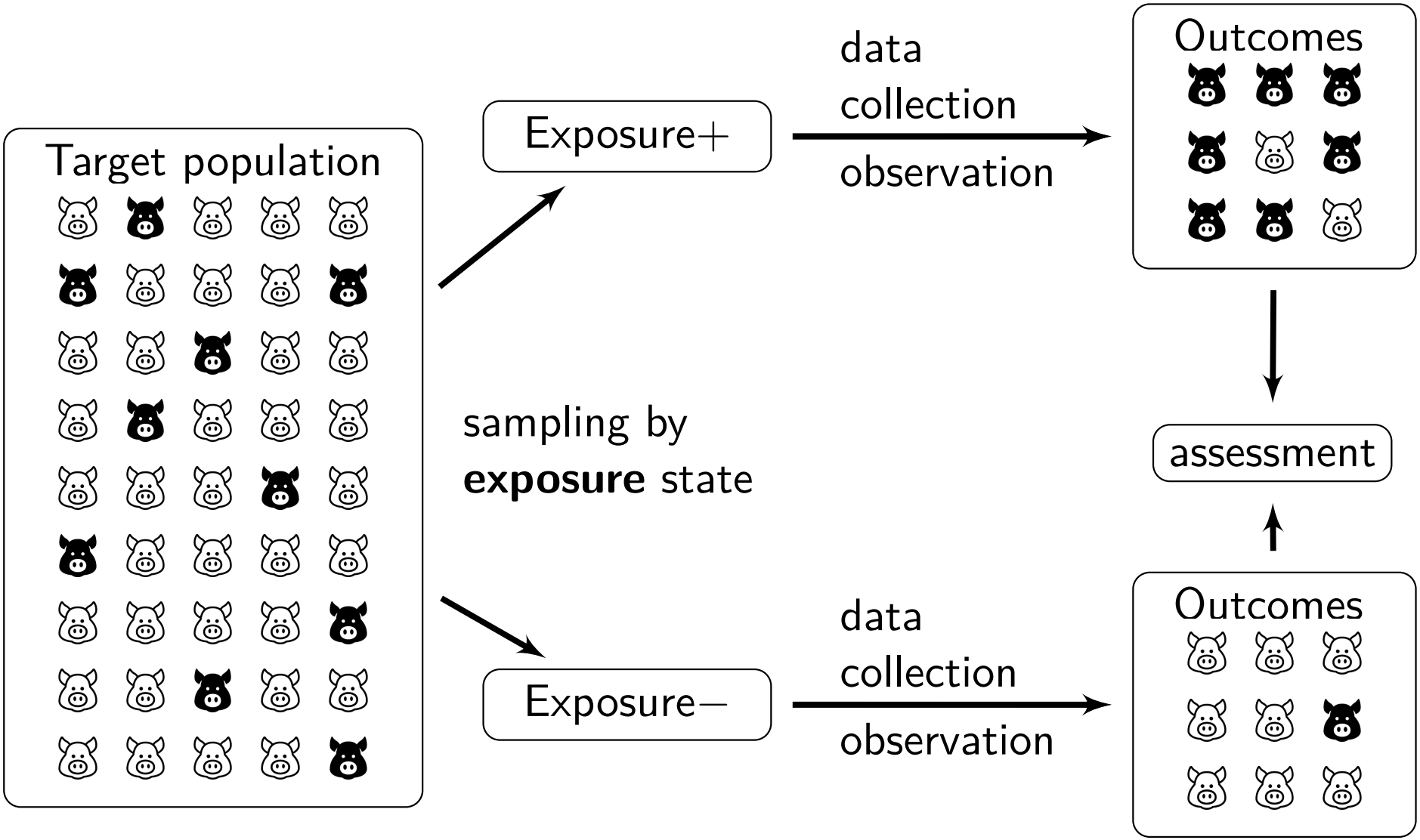
Cross-sectional study



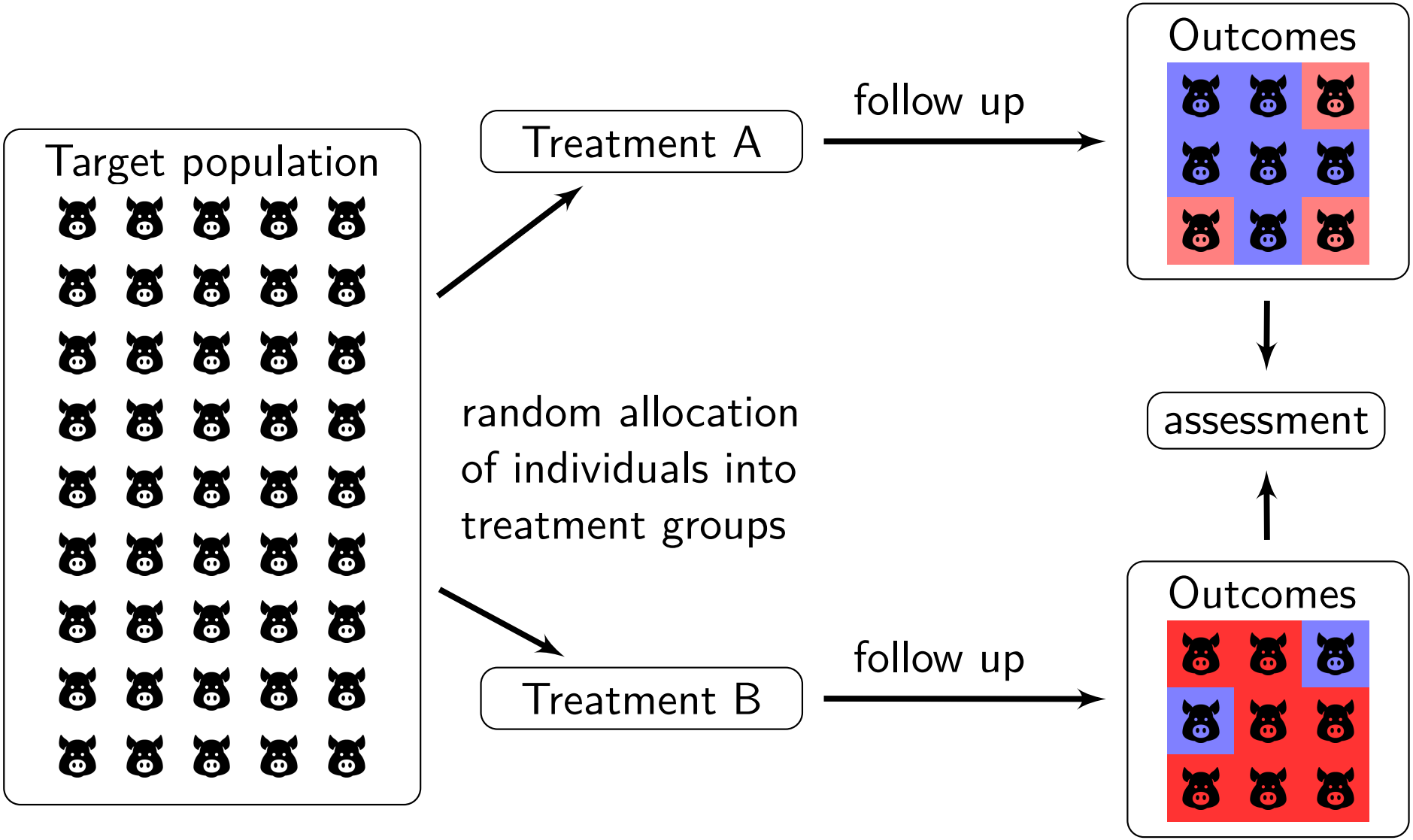
Case-control study



Cohors study



Randomized Controlled Trial (RCT)



Association?

- Lyme borreliosis
  - whether the risk of adverse pregnancy outcomes is associated by antibiotic treatment?(Lakos and Solymosi, 2010)
  - what are the association and its strongness between the age of foresters and seropositivity?(Lakos et al., 2012)
- Dirofilaria
  - have the warmer areas higher risk of D. immitis or D. repens occurrence?(Farkas et al., 2020)
- Endoscopic retrograde cholangiopancreatography
  - what is the relationship between the chance of post ERCP pancreatitis and the rectal administrated indomethacin?(Patai et al., 2015)
- Stillbirth
  - is the risk higher in heifer?(Szenci et al., 2018)
- COVID-19
  - whether obesity affects the recovery of COVID-19 patients?(Nakeshbandi et al., 2020)

Exposure

- Lyme borreliosis
  - whether the risk of adverse pregnancy outcomes is associated by antibiotic treatment?
  - what are the association and its strongness between the age of foresters and seropositivity?
- Dirofilaria
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  - whether obesity affects the recovery of COVID-19 patients?

Outcome

- Lyme borreliosis
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  - is the risk higher in heifer?
- COVID-19
  - whether obesity affects the recovery of COVID-19 patients?
- if we can identify factors that can be related to the outcome, it can be a base of controlling the disease (even if we don't know the exact causal chain)

The well known 2×2 table

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

dichotomous situation

The well known 2×2 table

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

The risk of the disease in the exposed group:

$$R_{E+} = \frac{a}{a+b}$$

The well known 2×2 table

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

The risk of the disease in the unexposed group:

$$R_{E-} = \frac{c}{c+d}$$

The well known 2×2 table

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

The risk of the disease in the whole population:

$$R_T = \frac{a+c}{a+b+c+d}$$

The well known 2×2 table

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

- Based on the R_{E+}, R_{E-} and R_T values, various association measures can be calculated.
- Main types:
  - measures of effect
  - measures of total effect
  - measures of therapeutic effect
  - measures of strength

Nakeshbandi et al. (2020) studied the effect of obesity on the recovery of COVID-19 patients (cohors design).

- 51 died of the 139 normal-weight patients
- 81 died of the 150 overweighted patients
- is there an association between death risk and obesity?
- if there is, how strong is it?

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- 51 died of the 139 normal-weight patients
- 81 died of the 150 overweighted patients
- is there an association between death risk and obesity?
- if there is, how strong is it?

	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$R_{E+} = \frac{81}{150} = 540 \text{ cases/1000}$$

$$R_{E-} = \frac{51}{139} = 367 \text{ cases/1000}$$

$$R_T = \frac{132}{289} = 457 \text{ cases/1000}$$

Nakeshbandi et al. (2020) studied the effect of obesity on the recovery of COVID-19 patients (cohors design).

- 51 died of the 139 normal-weight patients
- the incidence riskamong the normal-weight patients $R_{E-} = 51/139 = 367$ cases/1000

- 81 died of the 150 overweighted patients
- the incidence risk among the overweight patients $R_{E+} = 81/150 = 540$ cases/1000

- the incidence risk in the whole population $R_T = 132/289 = 457$ cases/1000

- is there an association between death risk and obesity?
- if there is, how strong is it?

cumulative incidence, cumulative mortality

Attributable risk (AR): the incidence risk of disease in the exposed that is attributable to exposure

$$AR = R_{E+} - R_{E-}$$

	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$R_{E+} = \frac{81}{150} = 540 \text{ cases/1000}$$

$$R_{E-} = \frac{51}{139} = 367 \text{ cases/1000}$$

$$AR = 540 - 367 = 173 \text{ cases/1000}$$

- describes the absolute frequency of disease associated with the exposure
- the incidence risk of death in overweight COVID-19 patients attributed to overweight is 173 cases/1000

Attributable fraction (AF): the proportion of disease in the exposed that is due to exposure

$$AF = \frac{R_{E+} - R_{E-}}{R_{E+}}$$

	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$R_{E+} = \frac{81}{150} = 540 \text{ cases/1000}$$

$$R_{E-} = \frac{51}{139} = 367 \text{ cases/1000}$$

$$AF = \frac{540 - 367}{540} = 0.32$$

- the proportion of disease in the exposed that is due to exposure
- 32% of death in overweight COVID-19 patients is attributable to overweight (AF=0.32)

Population attributable risk (PAR): the incidence risk of disease in the population attributable to exposure

$$PAR = R_T - R_{E-}$$

	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$R_{E-} = \frac{51}{139} = 367 \text{ cases/1000}$$

$$R_T = \frac{132}{289} = 457 \text{ cases/1000}$$

$$PAR = 457 - 367 = 90 \text{ cases/1000}$$

- the risk of death in COVID-19 patients that may be attributed to overweight is 90 cases/1000 (PAR=0.09)

Population attributable fraction (PAF): the proportion of disease in the population that is due to exposure

$$PAF = \frac{R_T - R_{E-}}{R_T}$$

	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$R_{E-} = \frac{51}{139} = 367 \text{ cases/1000}$$

$$R_T = \frac{132}{289} = 457 \text{ cases/1000}$$

$$PAF = \frac{457 - 367}{457} = 0.20$$

- 20% of death in COVID-19 patients is attributable to overweight (PAF = 0.20)

How would you describe the effect of the new drug?

Event rate the number of individual experiencing an event as a proportion of the number of individuals in the population

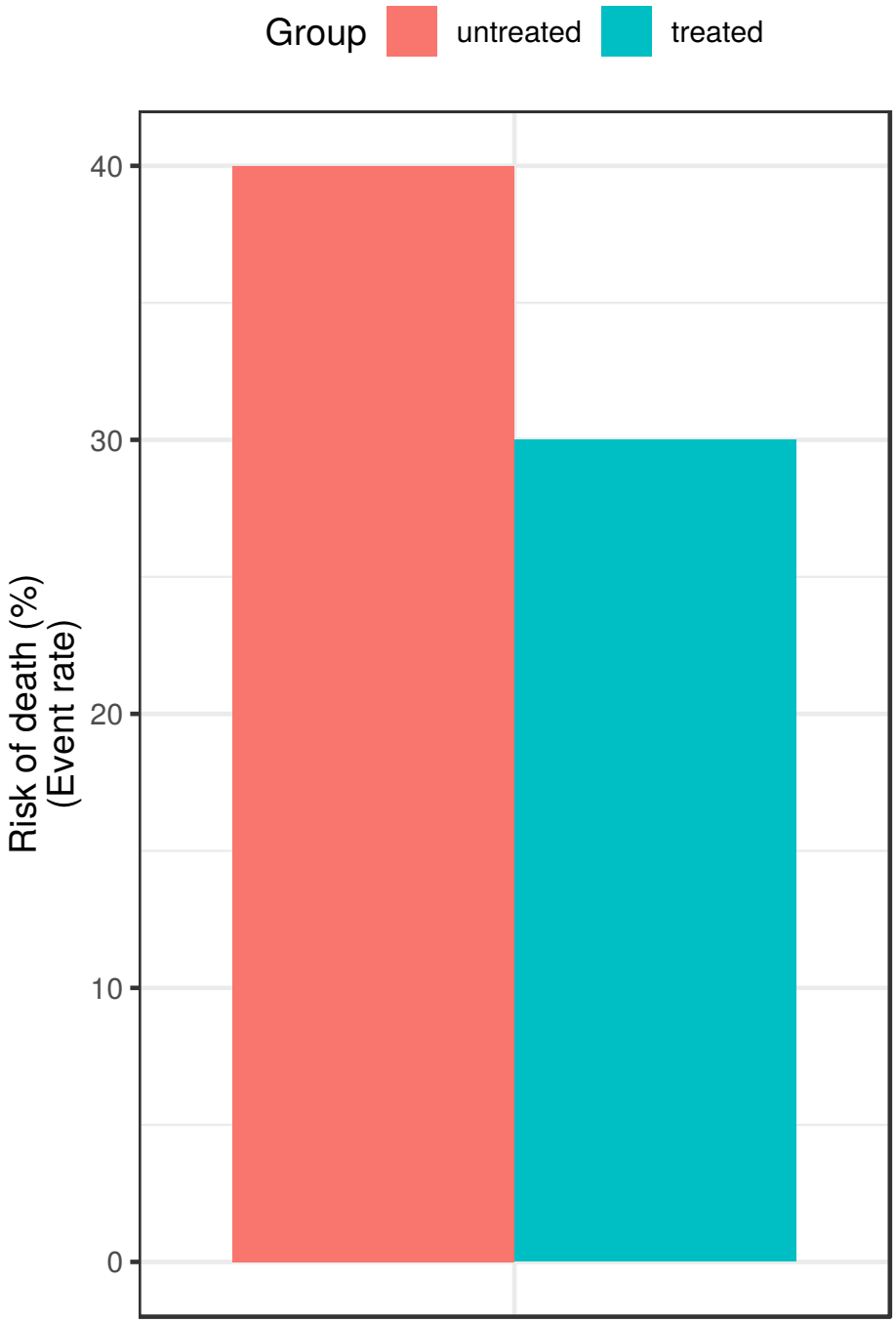
Absolute risk reduction, ARR the absolute difference between the untreated and treated group event rates

Absolute risk increase, ARI the absolute difference between the treated and untreated group event rates

Relative risk reduction, RRR the difference in event rates between 2 groups, expressed as a proportion of the event rate in the untreated group

Number needed to treat, NNT the number of patients who would have to receive the treatment for 1 of them to benefit ($NNT = 1/ARR$)

Number needed to harm, NNH the number of patients who would have to receive the treatment for 1 of them to experience an adverse effect ($NNH = 1/ARI$)



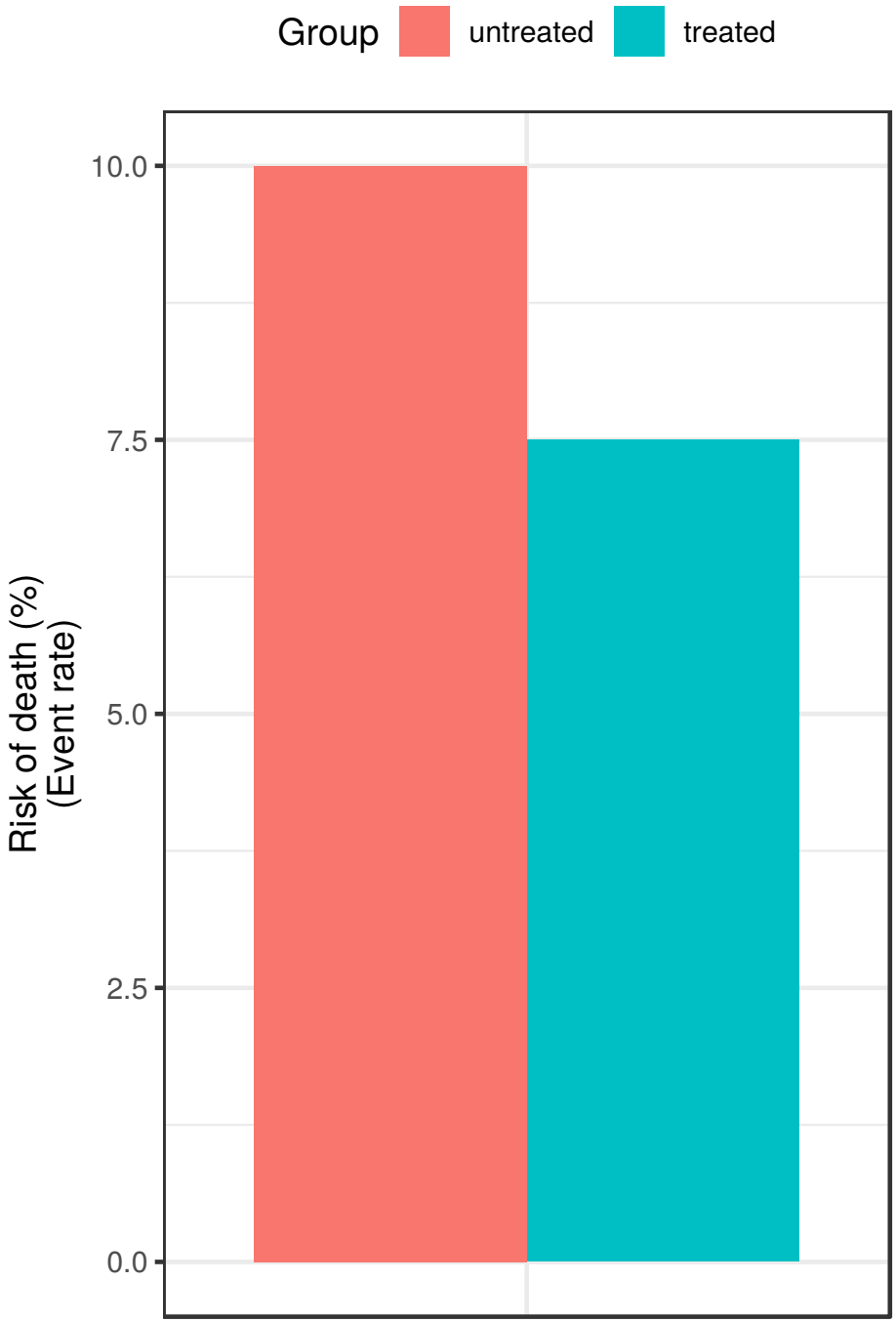
Suppose we study the effect of a new drug on COVID-19 patients with ***high-risk*** *(e.g. older men).*

Absolute risk reduction:

$$0.4 - 0.3 = 0.1$$

Relative risk reduction:

$$\frac{0.4 - 0.3}{0.4} = \frac{0.1}{0.4} = 0.25$$



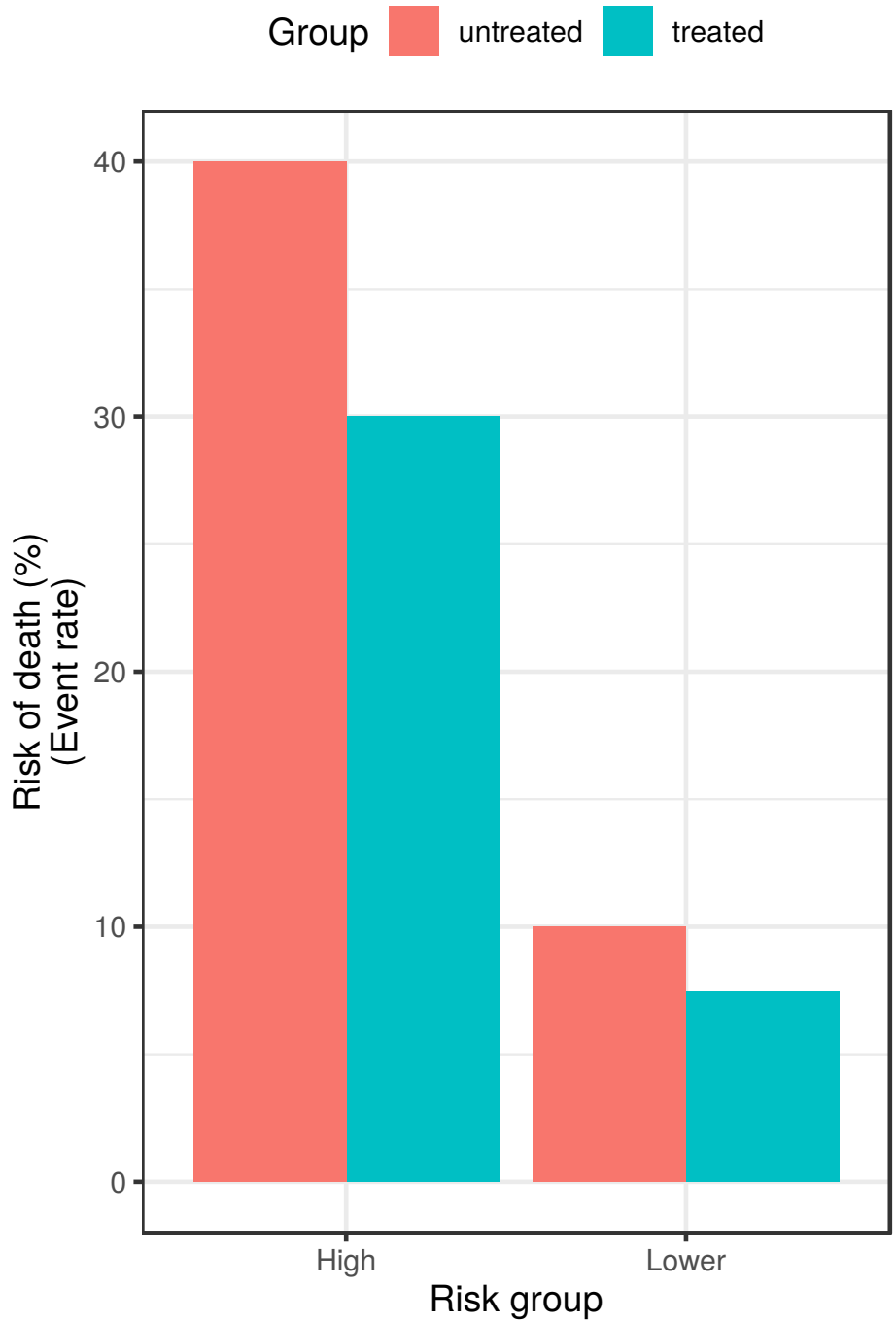
*The same medicine was used in a **lower risk** group (e.g. young women)*

Absolute risk reduction:

$$0.1 - 0.075 = 0.025$$

Relative risk reduction:

$$\frac{0.1 - 0.075}{0.1} = \frac{0.025}{0.1} = 0.25$$



Absolute risk reduction:

$$\text{High risk: } 0.4 - 0.3 = 0.1$$

$$\text{Low risk: } 0.1 - 0.075 = 0.025$$

Relative risk reduction:

$$\text{High risk: } \frac{0.4 - 0.3}{0.4} = 0.25$$

$$\text{Low risk: } \frac{0.1 - 0.075}{0.1} = 0.25$$

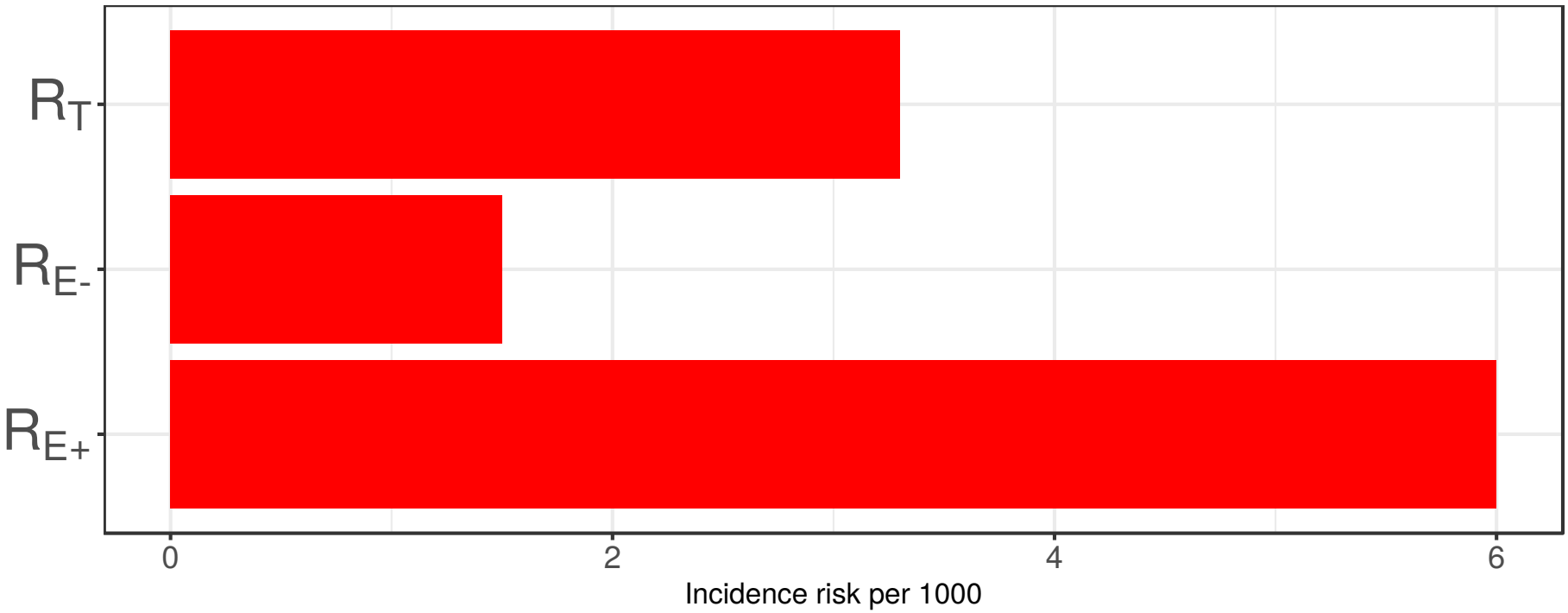
The **absolute** risk reduction becomes smaller when event rates are low, whereas the **relative** risk reduction, or "efficacy" of the treatment, often remains constant

Number needed to treat (NNT)

$$\text{High risk: NNT} = \frac{1}{0.4 - 0.3} = \frac{1}{0.1} = 10$$

$$\text{Low risk: NNT} = \frac{1}{0.1 - 0.075} = \frac{1}{0.025} = 40$$

- if the NNT for treatment is 10:
  - the practitioner would have to give the treatment to 10 patients to prevent 1 patient from having the adverse outcome
  - each patient who received the treatment would have a 1 in 10 chance of being a beneficiary
- if the absolute risk reduction is large, you need to treat only a small number of patients to observe a benefit in at least some of them
- if the absolute risk reduction is small, you must treat many people to observe a benefit in just a few



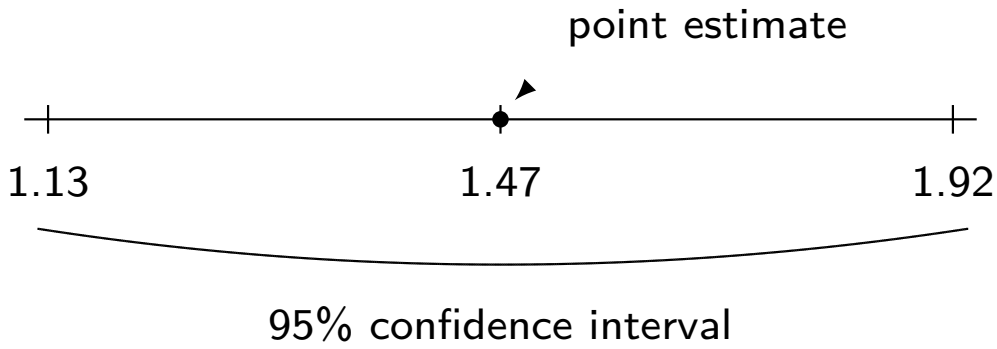
Relative risk (RR): the incidence risk of disease in the exposed divided by the incidence risk of disease in the unexposed

$$RR = \frac{R_{E+}}{R_{E-}} = \frac{0.54}{0.367} = 1.47 = 1.47$$

Incidence risk ratio

Interpretation: the incidence risk of death in overweight COVID-19 patients is 1.47 times higher than the incidence risk of death in normal-weight COVID-19 patients

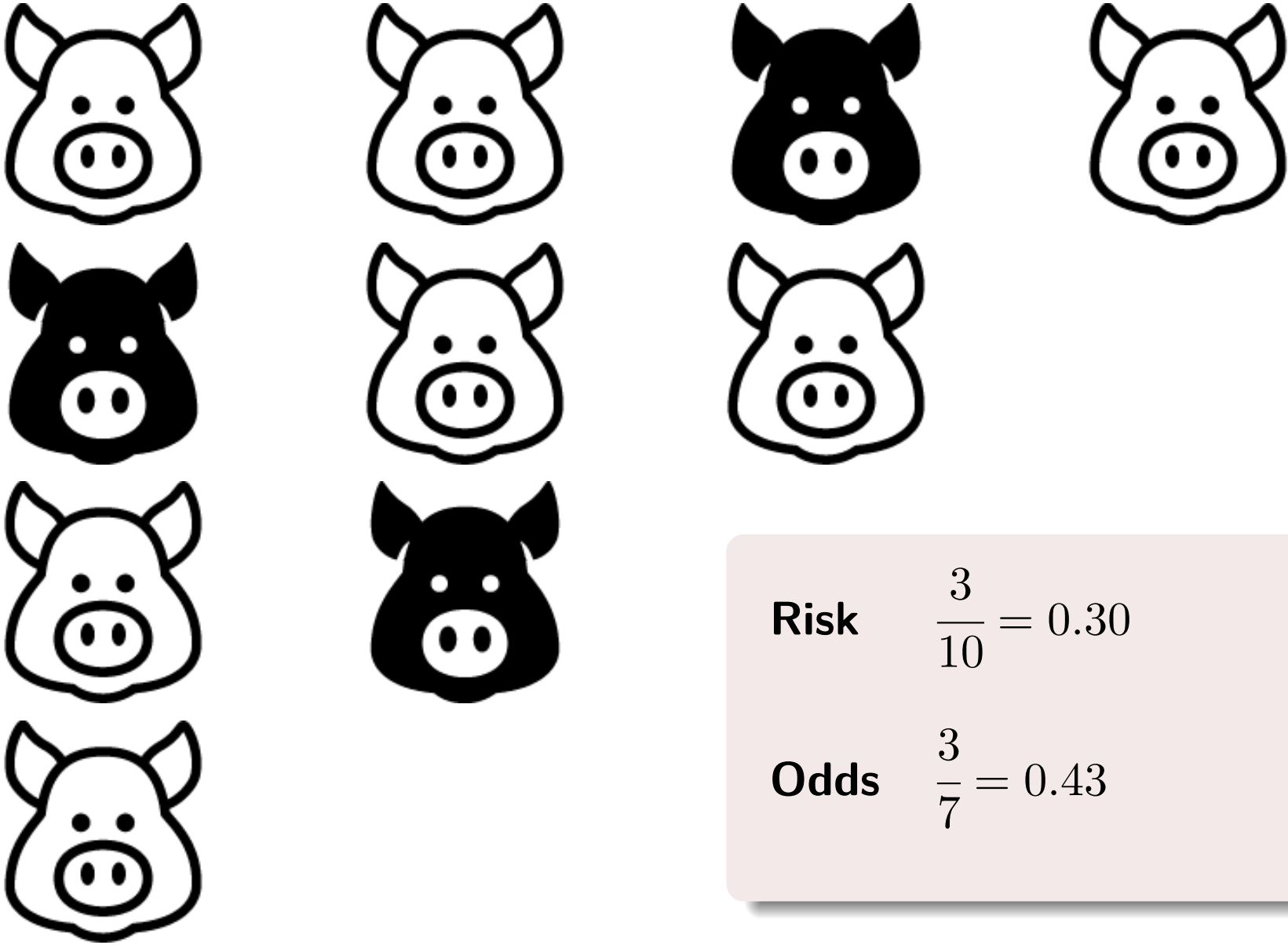
Reporting form: RR=1.47 (95% CI: 1.13 - 1.92).



When the time at risk is available, the incidence rate (IR) ratio is the **incidence rate** of disease in the exposed divided by the **incidence rate** of disease in the unexposed.

Incidence risk (or rate) ratio:

- provides an estimate of how many times more likely exposed individuals are diseased compared with non-exposed individuals
- if $RR = 1$:
  - then the risk of disease in the exposed and non-exposed groups are equal
- if $RR > 1$:
  - then exposure increases the risk of disease with greater departures from 1 indicative of a stronger effect
- if $RR < 1$:
  - then exposure (e.g. treatment) decreases the risk of disease
- can't be estimated in case-control studies, because we can't calculate incidence using case control data $\rightarrow$ OR



Risk $\frac{3}{10} = 0.30$

Odds $\frac{3}{7} = 0.43$

Odds ratio (OR): cohort studies

- the odds of disease in the exposed divided by the odds of disease in the unexposed

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

Odds in exposed group:

$$O_{E+} = \frac{a}{b}$$

Odds ratio (OR): cohort studies

- the odds of disease in the exposed divided by the odds of disease in the unexposed

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

Odds in unexposed group:

$$O_{E-} = \frac{c}{d}$$

Odds ratio (OR): cohort studies

- the odds of disease in the exposed divided by the odds of disease in the unexposed

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

Odds in whole population:

$$O_T = \frac{a+c}{b+d}$$

Odds ratio (OR): cohort studies

- the odds of disease in the exposed divided by the odds of disease in the unexposed

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

$$OR = \frac{O_{E+}}{O_{E-}}$$

$$O_{E+} = \frac{a}{b}, O_{E-} = \frac{c}{d}$$

Odds ratio (OR): cohort studies

- the odds of disease in the exposed divided by the odds of disease in the unexposed

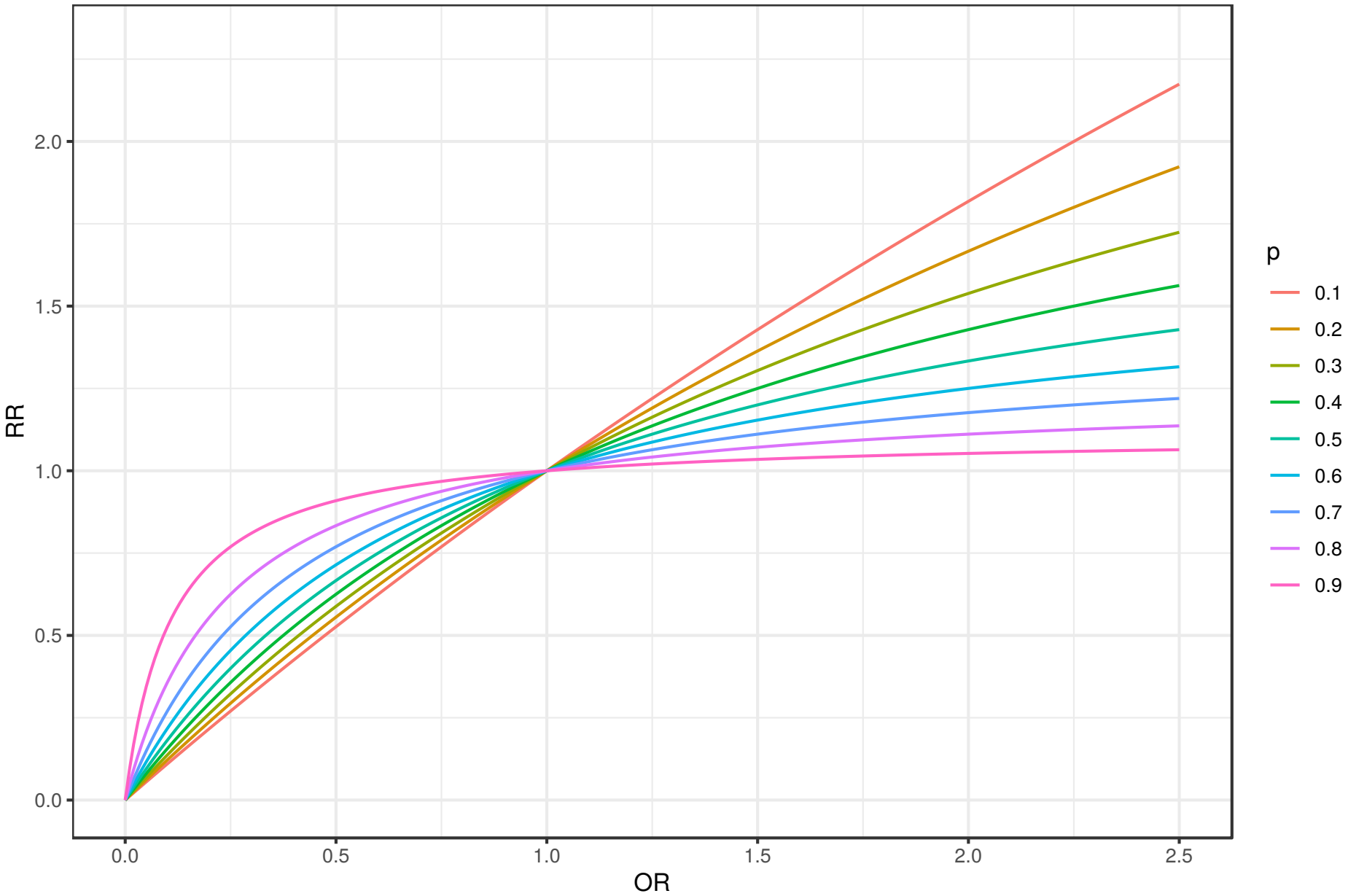
	Death+	Death−	$\sum$
Overweight	81	69	150
Normal	51	88	139
$\sum$	132	157	289

$$O_{E+} = \frac{81}{69} = 1.17$$

$$O_{E-} = \frac{51}{88} = 0.58$$

$$OR = \frac{1.17}{0.58} = 2.017 \text{ (95\% CI: 1.26 - 3.24)}$$

- the odds of adverse outcome, given exposure
- interpretation like RR


RR
OR
0.0
0.5
1.0
1.5
2.0
2.5
p
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

Odds ratio (OR): case-control studies

- the odds of exposure in the diseased divided by the odds of exposure in the undiseased

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

Odds in diseased group:

$$O_{D+} = \frac{a}{c}$$

Odds ratio (OR): case-control studies

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

Odds in disease free group:

$$O_{D-} = \frac{b}{d}$$

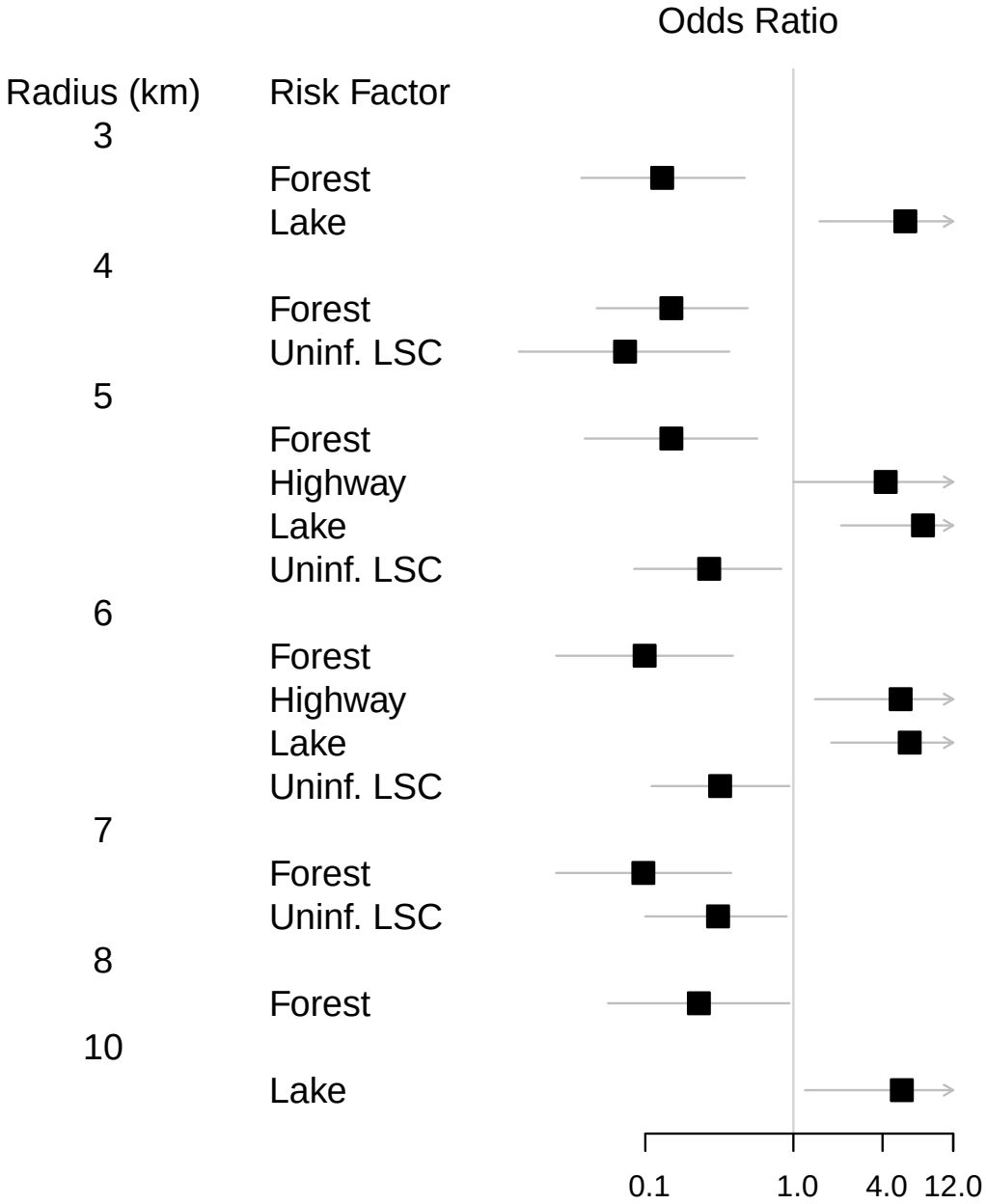
Odds ratio (OR): case-control studies

	Disease+	Disease−	$\sum$
Exposure+	a	b	$a+b$
Exposure−	c	d	$c+d$
$\sum$	$a+c$	$b+d$	$a+b+c+d$

$$OR = \frac{O_{D+}}{O_{D-}}$$

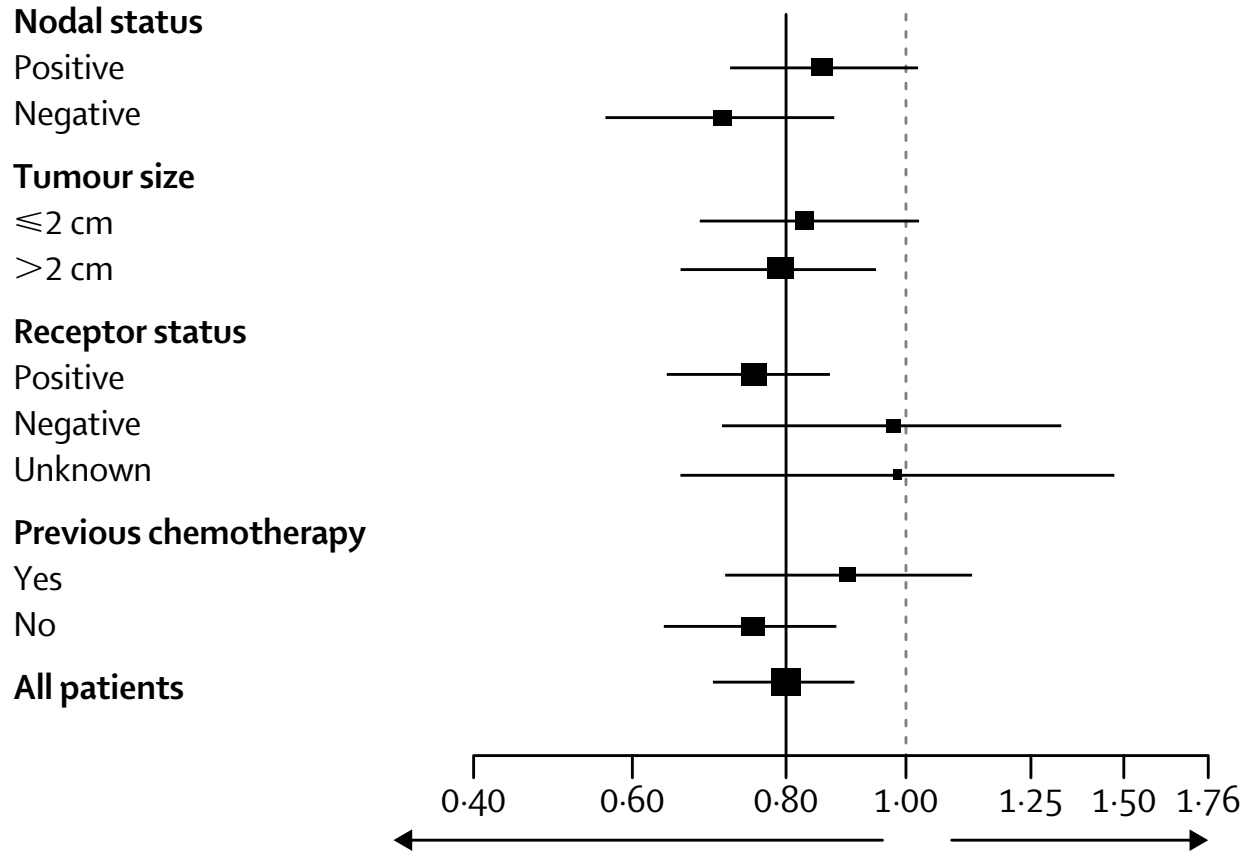
$$O_{D+} = \frac{a}{c}, O_{D-} = \frac{b}{d}$$

	Cohort study	Case-control study
Sequence		
	1. Define exposure status 2. Define disease status	1. Define disease status 2. Define exposure status
Measure of strength		
	RR or OR	OR
Interpretation of odds ratio		
	Odds of disease in exposed, compared with odds of disease in unexposed	Odds of exposure in diseased, compared with odds of exposure in undiseased



Final logistic multiple-regression models of risk factors (within indicated radii) for seropositivity of swine units for Aujeszky's disease in a county of Hungary, 1998–2000. (Uninf. LSC: Uninfected large-scale swine unit).

Solymosi et al. (2004)



Cuzick (2005)

- Confidence intervals in subgroups are always wider than those for the main effect because of smaller numbers.
- If the interval for a subgroup crosses the **no effect point**, this is widely misinterpreted as a lack of effect in the subgroup even where the overall effect is significant.
- Interpretation of subgroup effects would be helped if this line was deemphasised or omitted and replaced by a bold vertical line at the **overall treatment effect** level, making it easier to see if a subgroup confidence interval differed significantly from the overall effect.

	Adverse outcome		
	+	−	$\sum$
No treatment	6	4	10
Per os AB	6	13	19
$\sum$	12	17	29

Adverse outcome:

cavernous hemangioma, cerebral bleeding, dysplasia coxae, hypospadias, muscular hypotonicity, neonatal jaundice requiring exchange transfusion, papulovesicular eruption at birth, premature birth pyloric stenosis, skeletal anomaly, small for dates, spontaneous abortion, stillbirth

OR: 3.11, 95% CI: 0.51 - 21.60, p=0.2359

- if $p > 0.05$ and/or 95%CI contains the value 1.0, the result is not STATISTICALLY significant
- the p-value expresses the probability that the value of OR is at least 3.11 if the true odds ratio is equal to 1
- p-value is not the probability of H_0 is true (false); it expresses only the extremity of observed values assuming H_0

Lakos and Solymosi (2010)

```
m
```

```
       Treatment
Outcome  no  per os
      +   6       6
      -   4      13
```

```
fisher.test(m)
```

```
        Fisher's Exact Test for Count Data
data:  m
p-value = 0.2359
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.5125188 21.6033358
sample estimates:
odds ratio
  3.111034
```

```
(double_m = m*2)
```

```
       Treatment
Outcome  no  per os
      +  12      12
      -   8      26
```

```
fisher.test(double_m)
```

```
        Fisher's Exact Test for Count Data
data:  double_m
p-value = 0.05108
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.9190679 11.6961091
sample estimates:
odds ratio
  3.179755
```

- a negligible difference of p values may have a significant consequence (0.051, 0.049)

```
(triple_m = m*3)
```

```
       Treatment
Outcome  no  per os
      +  18      18
      -  12      39
```

```
fisher.test(triple_m)
```

```
        Fisher's Exact Test for Count Data
data:  triple_m
p-value = 0.01285
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 1.17897 9.04624
sample estimates:
odds ratio
  3.202991
```

Four hypothetical studies

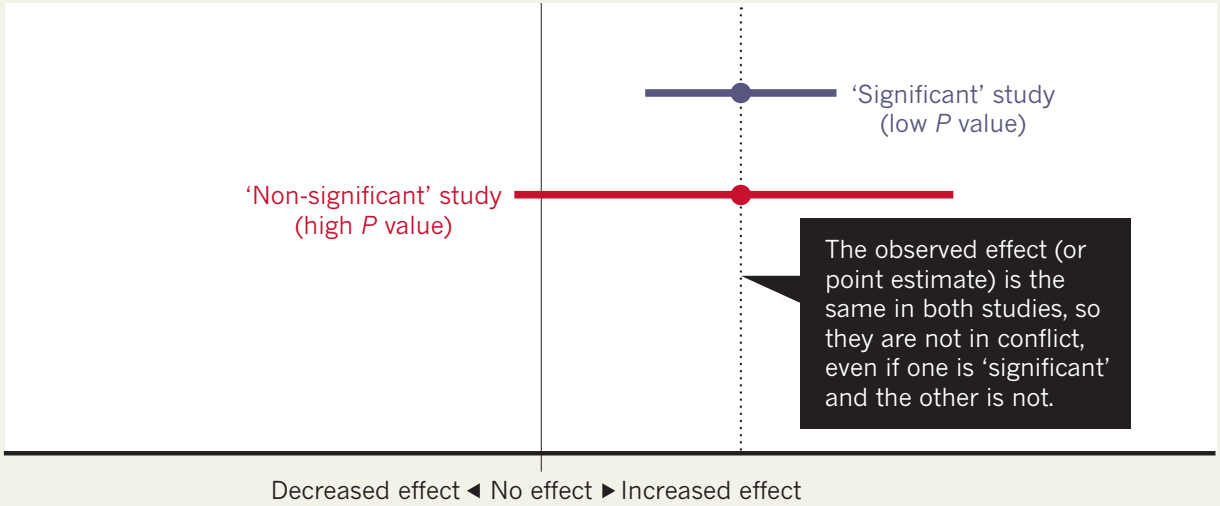
- patients are given treatments A and B and asked which they prefer
- p-values are equal

Number of patients receiving A or B	Numbers preferring $A : B$	% preferring A	two-sided p-value
20	15 : 5	75.00	0.04
200	115 : 86	57.00	0.04
2 000	1046 : 954	52.30	0.04
2 000 000	1 001 445 : 998 555	50.07	0.04

Spiegelhalter et al. (2004)

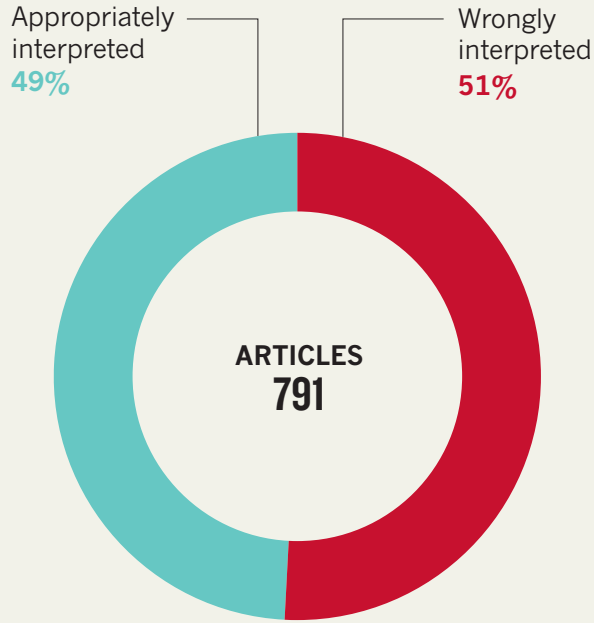
BEWARE FALSE CONCLUSIONS

Studies currently dubbed 'statistically significant' and 'statistically non-significant' need not be contradictory, and such designations might cause genuine effects to be dismissed.



WRONG INTERPRETATIONS

An analysis of 791 articles across 5 journals* found that around half mistakenly assume non-significance means no effect.



*Data taken from: P. Schatz *et al. Arch. Clin. Neuropsychol.* **20**, 1053–1059 (2005); F. Fidler *et al. Conserv. Biol.* **20**, 1539–1544 (2006); R. Hoekstra *et al. Psychon. Bull. Rev.* **13**, 1033–1037 (2006); F. Bernardi *et al. Eur. Sociol. Rev.* **33**, 1–15 (2017).

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