Introduction to biostatistics: Part 2. Measures of association as used to address therapy, harm, and etiology questions

WHAT ARE MEASURES OF ASSOCIATION?

Measures of association describe the strength of the relation between an exposure (or intervention) and an outcome in clinical studies (randomized controlled trials, cohort studies, and case–control studies). There are 2 types of measure: *relative* (relative risk, relative risk reduction, and odds ratio) and *absolute* (absolute risk reduction and number needed to treat).

Confidence intervals (CIs) should be given for each measure of association to quantify their uncertainty and are usually reported as 95% CI (i.e., the interval has a 95% chance of including the true, but unknown, population value). If the 95% CI overlaps the value of no effect, the result is not statistically significant at the 5% level.

The identification of a statistically significant association between an exposure and an outcome alone does not imply causation. Possible bias and consistency need to be considered (1–3). When addressing therapy, harm, or etiology questions, a systematic review of ≥ 2 double-blind RCTs typically provides more convincing evidence than an individual RCT, which again provides more convincing evidence than an individual cohort or case–control study.

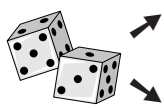
WHEN ARE THEY USED?

All of the absolute and relative measures of association described above can be used in RCTs and cohort studies. However, in case–control studies, only odds ratios should be calculated because in such a study the prevalence of the outcome (e.g., disease) is not known because the groups are determined by outcome rather than exposure status.

HOW ARE THEY CALCULATED?

The most common measures are calculated in the Table using the results from probably the earliest RCT (4).

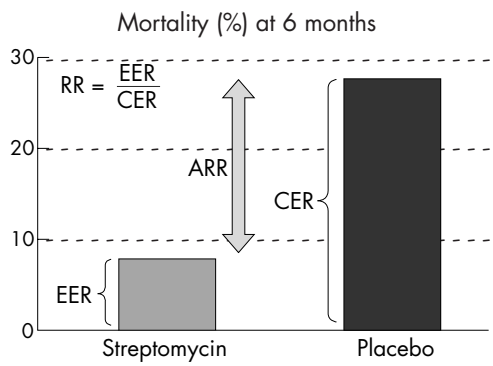
Streptomycin vs placebo

Patients	Randomization	Intervention	Outcome at 6 mo	
			Alive	Dead
107 men and women 15 to 30 years of age with acute bilateral pulmonary tuberculosis		Streptomycin + bed rest ($n = 55$)	51	4
		Placebo + bed rest ($n = 52$)	38	14

Q: What proportion died on streptomycin?
4 of 55 (7.3%).
This percentage is called the experimental event risk (EER).

Q: What proportion died on placebo?
14 of 52 (26.9%).
This percentage is called the control event risk (CER).

Some authors call the EER and CER "rates" instead of risks, which is technically inaccurate as rates describe the number of events per person over time (Figure).



Experimental and control event risks.

ABSOLUTE RISK REDUCTION (ARR)

Q: What was the difference in risk of death between the 2 groups?

19.6% (95% CI 5.7% to 33.6%) more people died on placebo than streptomycin. This result is statistically significant at the 5% level because the 95% CI does not overlap the value of no effect (ARR = 0%).

This is called the absolute risk reduction (ARR) and is calculated by subtracting the EER from the CER.

$$ARR = CER - EER = 26.9\% - 7.3\% = 19.6\%$$

When positive outcomes are considered (e.g. survival) and the intervention is more helpful than the control, this is called the absolute benefit increase (ABI).

NUMBER NEEDED TO TREAT (NNT)

Q: How many people with tuberculosis would I need to treat with streptomycin to prevent 1 additional death?

6 (95% CI 3 to 18) patients with tuberculosis would need to be treated with streptomycin to prevent one *additional* person dying. This result is statistically significant at the 5% level because the 95% CI does not overlap the value of no effect (NNT = infinity when ARR = 0%). The word "additional" is used to stress the fact that not everybody died on placebo.

This measure is called the number needed to treat (NNT). The NNT is usually rounded up to the nearest whole number to provide a more conservative estimate of the added value of the intervention.

The NNT is the reciprocal of the ARR.

$$NNT = 1 \div ARR = 1 \div 19.6\% = 1 \div (19.6 \div 100) = 5.1 = 6$$

A negative NNT is also known as the number needed to harm (NNH).

RELATIVE RISK (RR)

Q: What was the risk for dying on streptomycin relative to placebo?

The bar graph shows that for every 1 patient who died on streptomycin, approximately 4 patients died on placebo (27 ÷ 7).

This is called the relative risk (RR). The RR compares the risk for death in the intervention group (EER) with the risk for death in the control group (CER).

$$RR = EER \div CER = 7.3\% \div 26.9\% = 0.27$$

The RR for dying on streptomycin compared with placebo was 0.27 (CI 0.10 to 0.77). This result is statistically significant at the 5% level because the 95% CI does not overlap the value of no effect (RR = 1).

RELATIVE RISK REDUCTION (RRR)

Q: How much less common was death on streptomycin compared with placebo?

Treatment with streptomycin was associated with a 73% (CI 23% to 90%) reduction in the risk for death compared with placebo. In other words, antibiotic treatment prevented approximately three quarters of the deaths that would have occurred on placebo. This result is statistically significant at the 5% level because the 95% CI does not overlap the value of no effect (RRR = 0%).

This is called the relative risk reduction (RRR) and is commonly used in promotional literature from pharmaceutical companies.

The RRR can be calculated by either dividing the ARR by the CER or subtracting the RR from 1.

$$RRR = 1 - RR = ARR \div CER = 19.6\% \div 26.9\% = 0.73 = 73\%$$

When positive outcomes are considered and the intervention is more helpful than the control, this is called the relative benefit increase (RBI).

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