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Measures of effect: Relative risks, odds ratios, risk difference, and 'number needed to treat'

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Epidemiological studies aim at assessing the relationship between exposures and outcomes. Clinicians are interested in knowing not only whether a link between a given exposure (e.g. smoking) and a certain outcome (e.g. myocardial infarction) is statistically significant, but also the magnitude of this relationship. The 'measures of effect' are indexes that summarize the strength of the link between exposures and outcomes and can help the clinician in taking decisions in every day clinical practice. In epidemiological studies, the effect of exposure can be measured both in relative and absolute terms. The risk ratio, the incidence rate ratio, and the odds ratio are relative measures of effect. Risk difference is an absolute measure of effect and it is calculated by subtracting the risk of the outcome in exposed individuals from that of unexposed.

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This study addresses the measures of effect, that is, the measures that are used to compare the frequency of disease (or other outcome) between two groups. The measures of effect are generally expressed as relative risks and odds ratios (OR) (relative measures of effect) or as risk difference (absolute measure of effect). The 'number needed to treat' (NNT) is another absolute measure of effect that is frequently used in clinical trials.

RELATIVE MEASURES OF EFFECT

The relative risk

The relative risk can be calculated as ratio between two incidence proportions (risk ratio, see Example 1) or two incidence rates (incidence rate ratio, see Example 2).

Example 1: In the randomized prospective, Heart Outcomes Prevention Evaluation (HOPE) study,[1] the effect of ramipril on the risk of cardiovascular (CV) events, was investigated by calculating the ratio between the incidence proportions of CV events in ramipril-treated and in placebo-treated patients.

	With CV events	Without CV events
Ramipril group (*n*=4645)	651	3994
Placebo group (*n*=4652)	826	3826

Proportion of patients with CV events in the ramipril group: 651/4645=0.14 (14%). Proportion of patients with CV events in the placebo group: 826/4652=0.18 (18%). The risk ratio is 0.14/0.18=0.78.

A value of 0.78 indicates that patients treated with ramipril had a lower risk than untreated patients and that this drug induced a 22% decrease in the risk of CV events (relative risk reduction).

The confidence interval

The risk ratio (as well as other measures of effect) is generally accompanied by a measure of the precision of the estimate: the confidence interval (CI). In the HOPE study, the CI was 0.70–0.86. The concept of the CI can be explained as follows: if 100 samples of the same size considered in the HOPE study would be drawn from the population and if we would calculate for each sample the risk ratio associated with

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ramipril treatment, we would obtain a 100 (all slightly different) risk ratio estimates. The 95% CI is the interval that includes the 95% of risk ratios of these 100 population samples. Thus, the 95% CI is the interval of values in which the true risk ratio is likely to lie with a probability of 95%. To be statistically significant with a $P<0.05$, a risk ratio should have a 95% CI not including 1.0. Thus, in the HOPE study, the risk ratio of 0.78 (95% CI 0.70–0.86) is statistically significant.

Example 2: Parekh *et al.*[2] investigated the risk of new atherosclerotic complications according to race in a prevalent population of end-stage renal disease patients. They reported the relative risk for peripheral vascular disease in white as compared to black dialysis patients in terms of incidence rate ratio.

	Incidence rate of peripheral vascular disease (Events/1000 person-years)
Whites	114
Blacks	109

The incidence rate ratio is defined as the incidence rate of disease occurrence in the exposed group divided by the incidence rate of disease occurrence in the unexposed group (the calculation of incidence rate is reported in the first paper of this series).[3] In the Parekh's study, the incidence rate ratio was calculated as: 114/109 = 1.05 (95% CI 0.95–1.16). Thus, in this sample, white dialysis patients have an incidence rate of peripheral vascular disease that is 5% higher than that in blacks, but this excess risk did not attain the formal statistical significance (the 95% CI included 1.0). A 95% CI including 1 means that there is not sufficient, probabilistic evidence that the excess risk for peripheral vascular diseases in whites than in blacks is true, in the universe of patients, with a 95% probability (i.e. there is a probability >5% that this effect is due to random error, i.e. the error purely attributable to chance).

The odds ratio

The odds are a way of representing probability, familiar to gamblers. For example, the odds that a single throw of a die produces a six are 1–5, that is 1 chance of success and 5 chances of failure (see Example 3). In a case–control study, the odds of exposure in cases and controls are calculated as the number of exposed individuals divided by the number of unexposed individuals in each group. If we know the odds of exposure in cases and controls, we can calculate the OR, that is the ratio between the odds of exposure in diseased and in non-diseased individuals. As discussed for the risk ratio, an OR<1.0 implies that the risk of the outcome is lower in exposed individuals than in unexposed individuals; vice versa an OR>1.0 means that the odds are higher in exposed individuals.

Example 3: Knoll *et al.*[4] investigated the association between vascular access thrombosis and thrombophilia. They considered 107 patients with access thrombosis (cases) and 312 patients without fistula thrombosis (controls). Overall, among the 107 patients with access thrombosis, 59 had evidence of thrombophilia and 48 did not, while among the 312 without access thrombosis 122 had thrombophilia and 190 did not.

- Odds of thrombophilia in patients with vascular access thrombosis: 59/48 = 1.229.
- Odds of thrombophilia in patients without vascular access thrombosis: 122/190 = 0.642

The OR is 1.229/0.642 = 1.91.

An odds ratio of 1.91 means that the odds of exposure to thrombophilia were 91% higher in patients with vascular access thrombosis than in those without this complication. This OR was statistically significant because the 95% CI of this estimate (95% CI 1.23–2.98) did not include 1. The authors concluded that although large, multicenter, prospective cohort studies are needed to confirm this observation, thrombophilia seems to be associated with vascular access thrombosis in hemodialysis patients.

To understand why the risk ratio is not appropriate in the Knoll's study, we consider the example reported in Figure 1, showing that, unlike the OR, the risk ratio among others depends on the number of controls taken for each case. As shown in Figure 1 (left panel), the risk ratio for arteriovenous fistula thrombosis results to be 65% higher (risk ratio = 1.65) in patients with thrombophilia than in those without this complication. Now, as an example, we consider the following hypothetical situation. If, to increase the study power, the

Thrombophilia	With AV fistula thrombosis	Without AV fistula thrombosis	
Yes	59	122	59+122=181
No	48	190	48+190=238
OR=(59/48)/(122/190)=1.91 Risk ratio=(59/181)/(48/238)=1.65			

Thrombophilia	With AV fistula thrombosis	Without AV fistula thrombosis	
Yes	59	244	59+244=303
No	48	380	48+380=428
OR=(59/48)/(244/380)=1.91 Risk ratio=(59/303)/(48/428)=1.77			

Figure 1 | Left panel: Schematic representation of the Knoll's study.[4] Right panel: by starting with the Knoll's study we created a hypothetical situation in which only the number of controls was doubled. As shown in the figure, on changing the number of controls the risk ratio increases from 1.65 to 1.77, while the OR remains unchanged. The gray area identifies controls.

investigator had decided to double the number of controls, hypothesizing that the exposure in this larger control group remains the same of that of the original control group, the risk ratio would have increased from 1.65 to 1.77 (!) (Figure 1, right panel). In contrast, the OR did not change in respect to the risk ratio (Figure 1). This is because of the way the two measures of effect are calculated. In fact, the incidence proportion (by which we calculate the risk ratio) is dependent on the number of both cases and controls and exposed and unexposed individuals while the odds, being a within-group absolute risk indicator, is only affected by the distribution of exposure in each group. Since the allocation fraction of the exposure in the larger control group did not change in respect to the original control group, the OR remained unchanged. OR is a good estimate of risk ratio when the disease/event is rare (rare disease assumption).[5]

ABSOLUTE MEASURES OF EFFECT

Risk difference (or absolute risk reduction)

The effect associated to a specific treatment can be also calculated in terms of absolute risk difference. The calculation is just the difference between the incidence proportion of a disease/event in the control group and the incidence proportion of the same outcome in the treated group. Accordingly, in the HOPE study, the risk difference for CV events between patients on placebo and on ramipril is: 0.18–0.14 = 0.04 (i.e. 4% absolute risk difference attributable to ramipril).

NNT

On the basis of the risk difference it is possible to calculate the NNT to prevent one adverse event. In the HOPE study, the number of patients to be treated to prevent one CV event in 5 years can be calculated as the inverse of the absolute risk difference (NNT = 1/absolute risk difference): 1/0.04 is 25. So, we ought to treat 25 patients with ramipril to prevent one CV event in 5 years. The ideal NNT for a given treatment is 1. In fact a NNT = 1 means that all treated individuals had a favorable outcome (i.e. had no events: incidence proportion = 0), while all untreated individuals had adverse outcome (i.e. experienced the event in question: incidence proportion = 1). If the number of events in the HOPE study had been 65 in ramipril group and 83 in placebo group (instead of 650 and 826, respectively), the NNT would have been 1/(0.018–0.014) = 250, while the RR would have remained unchanged (RR = 0.014/0.018, i.e. 0.78). Thus, the NNT provides a good insight into the clinical relevance of the effect.

CONCLUSION

To estimate the magnitude of the association between exposure and outcomes we can use relative and absolute measures of effect. Relative measures of effect are risk ratio (i.e. the ratio between two incidence proportions), incidence rate ratio (the ratio between two incidence rates), and OR (the ratio between two odds). The risk difference is an absolute measure of effect (i.e. the risk of the outcome in exposed individuals minus the risk of the same outcome in unexposed). The risk difference is frequently used in clinical trials to calculate the NNT, that is the number of individuals that is needed to treat to prevent one adverse event in a given time period.

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