Small studies

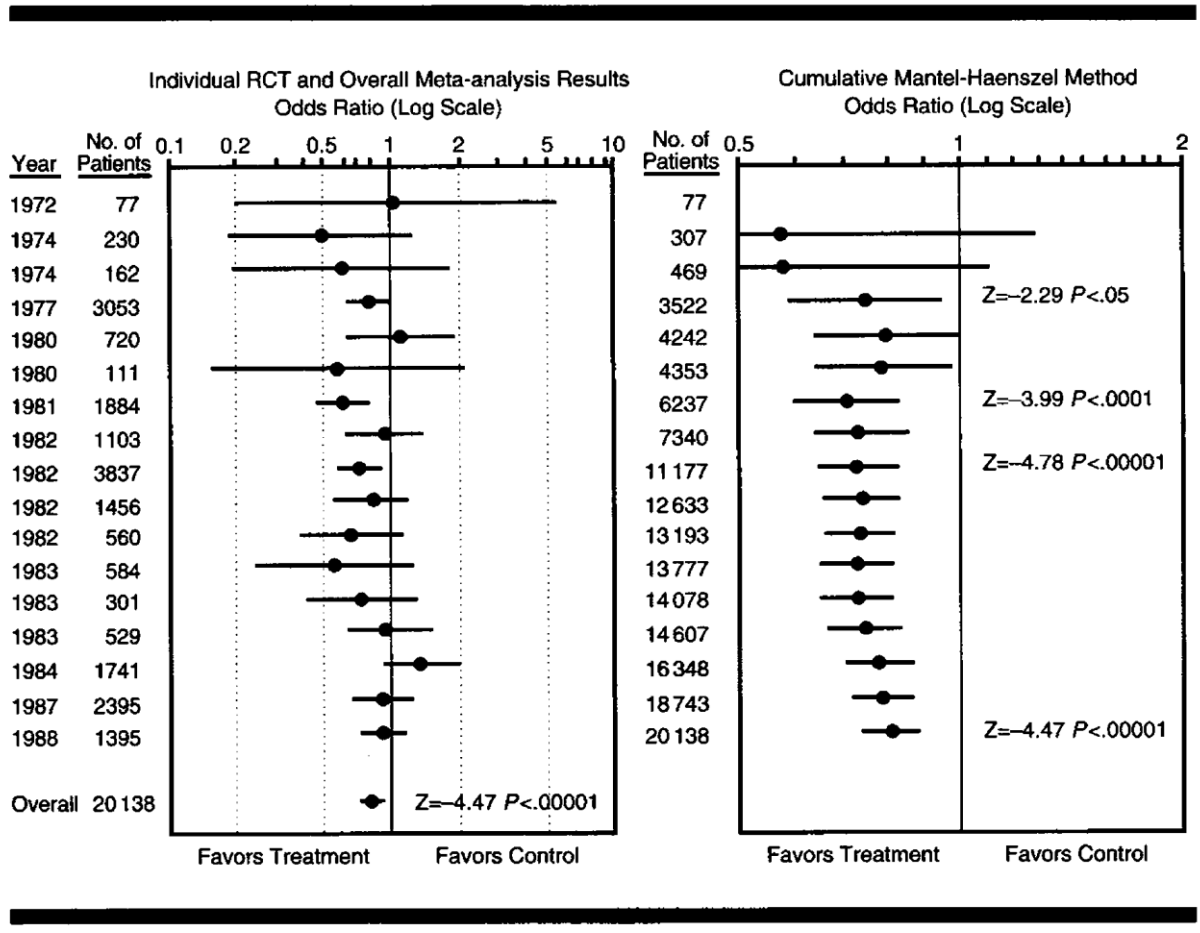
From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

2.4a Be cautious of small studies.

Explanation

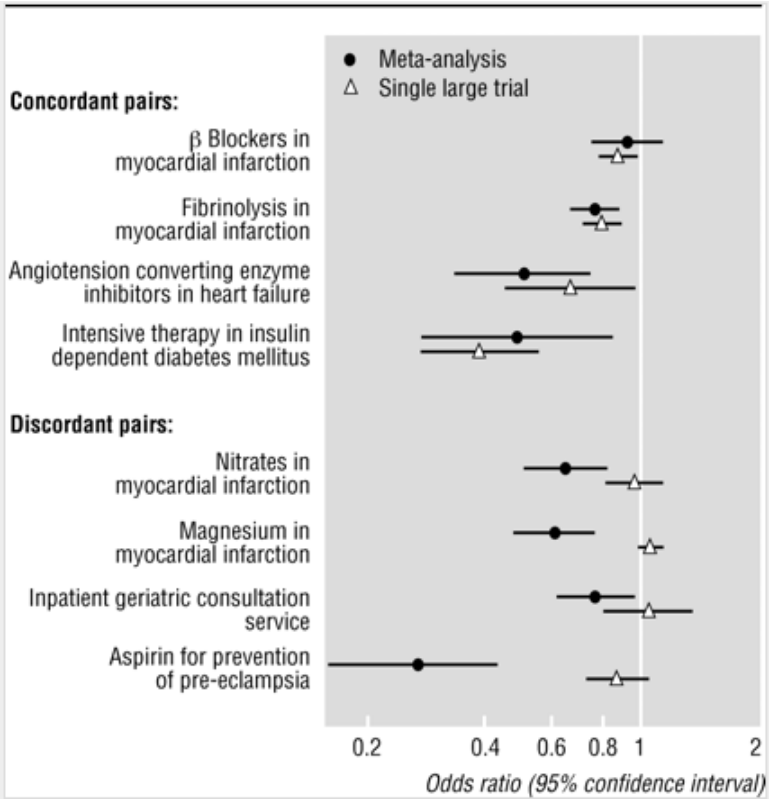
When there are few outcome events, differences in outcome frequencies between the treatment comparison groups may easily have occurred by chance and may mistakenly be attributed to differences in the effects of the treatments, or the lack of a difference.

For example, by 1977 there were at least four randomized trials that compared the number of deaths in patients given a beta-blocker to patients given a placebo. Beta-blockers are medicines that work by blocking the effects of epinephrine (also known as adrenaline). There was a small number of deaths in each study and the results appeared to be inconsistent, as can be seen in the figure on the left below *[Antman 1992 (SR)]*. The results of individual studies continued to vary up until 1988. However, as can be seen in the figure on the right below, if the results of the available studies were combined, the overall estimate (across studies) changed very little after 1977. It simply became more precise. This is indicated by the horizontal lines, which show the confidence intervals for each effect estimate.



In the example above, the variation in effect estimates may have occurred largely by chance alone. The overall effect estimate across the small studies was consistent with the results of a large randomized trial with a low risk of bias published in 1986 *[Egger 1997]*. However, effect estimates from small studies may overestimate actual effects. There are several possible reasons for this. Compared to large studies, small studies may be more prone to publication bias and reporting bias, may have a higher risk of bias because of the design of the studies. Small studies also may include more highly selected participants and may implement treatments more uniformly.

For example, in some countries, intravenous (IV) magnesium was administered to heart attack patients to limit damage to the heart muscle, prevent serious arrhythmias and reduce the risk of death. A controversy erupted in 1995, when a large well-designed trial with 58,050 participants did not demonstrate any beneficial effect to IV magnesium, contradicting earlier meta-analyses of the smaller trials. The figure below shows four examples where the results of small trials were consistent with the results of a single large trial (concordant pairs) and four examples where they were not consistent (discordant pairs), including IV magnesium for acute heart attacks *[Egger 1997]*.



It is difficult to predict when or why effect estimates from small studies will differ from effect estimates from large studies with a low risk of bias or to be certain about the reasons for differences. However, systematic reviews should consider the risk of small studies being biased towards larger effects and consider potential reasons for bias in effect estimates from small studies. A systematic review published in 2007 included 26 randomized trials that compared IV magnesium to an inactive substance (placebo) *[Li 2007 (SR)]*. IV magnesium reduced the incidence of serious arrhythmias, but also increased the incidence of profound hypotension, bradycardia and flushing. The apparent large effect of magnesium on reducing the number of deaths may have reflected various biases in smaller trials.

Basis for this concept

A systematic review of 93 meta-analyses found that effect estimates differed within meta-analyses based on their size, with larger effect estimates seen in small to moderately sized trials compared to the largest trials *[Dechartres 2013 (SR)]*. Another systematic review found that smaller studies reported larger effects in 19% of the 5,534 meta-analyses with ≥10 studies *[Schwab 2021 (SR)]*. Only 4% of those meta-analyses showed evidence of publication bias. The extent to which small studies reported larger effects varied across medical specialities. Other systematic reviews have also found that small studies sometimes overestimate treatment effects *[Ioannidis 2007 (SR), Lin 2020 (SR), Nüesch 2010 (SR)]*.

There are several reasons why small studies may overestimate treatment effects *[Egger 1997 , Schwab 2021 (SR)]*. One reason is reporting: small studies may be more prone to publication bias and selective outcome reporting (reporting bias). Another reason is that small studies may have a higher risk of bias due to their design and implementation compared to large studies. Also, large studies may include more diverse patients and implementation of treatments (making them more "pragmatic") compared to small studies (which may be more "explanatory"). It may be difficult to detect when small studies overestimate treatment effects [Ioannidis 2007 (SR)], and to detect the reasons for them overestimating or potentially overestimating effects.

Implications

Be cautious about relying on the results of treatment comparisons with few outcome events. The results of such comparisons can be misleading.

References

Systematic reviews

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